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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1996

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BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTH CONGRESS

FIRST SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

JOHN EDWARD PORTER, Illinois, *Chairman*

C. W. BILL YOUNG, Florida	DAVID R. OBEY, Wisconsin
HENRY BONILLA, Texas	LOUIS STOKES, Ohio
ERNEST J. ISTOOK, JR., Oklahoma	STENY H. HOYER, Maryland
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FRANK RIGGS, California	
ROGER F. WICKER, Mississippi	

NOTE: Under Committee Rules, Mr. Livingston, as Chairman of the Full Committee, and Mr. Obey, as Ranking Minority Member of the Full Committee, are authorized to sit as Members of all Subcommittees.

S. ANTHONY MCCANN, ROBERT L. KNISELY, SUSAN E. QUANTIUS, MICHAEL K. MYERS, and JOANNE L. ORNDORFF, *Subcommittee Staff*

PART 4

NATIONAL INSTITUTES OF HEALTH

Printed for the use of the Committee on Appropriations

OCT 19 1995

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1996

HEARINGS

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1996

TUESDAY, FEBRUARY 28, 1995.

NOBEL LAUREATES BIOMEDICAL RESEARCH PANEL

WITNESSES

J. MICHAEL BISHOP, M.D., UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIFORNIA

MICHAEL S, BROWN, M.D., DEPARTMENT OF MOLECULAR GENETICS, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, DALLAS, TEXAS

DAVID HUBEL, M.D., DEPARTMENT OF NEUROBIOLOGY, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

JOSEPH E. MURRAY, M.D., HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

PHILLIP A. SHARP, Ph.D., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASSACHUSETTS

JAMES D. WATSON, Ph.D., DIRECTOR, COLD SPRING HARBOR LABORATORY, COLD SPRING HARBOR, NEW YORK

Mr. PORTER. The subcommittee will come to order.

This morning we are pleased to revive a tradition of the subcommittee from the 1980s. We have invited six Nobel laureates to come and speak with the subcommittee to give us their perspectives on the achievements and the possibilities of biomedical research. We do not have a specific agenda; we are simply here to gather knowledge from eminent scientists and to provide a prelude to our hearings on the NIH budget in March.

We are especially looking forward to hearing from those who are among the most distinguished researchers of our country, and we acknowledge also the presence of Dr. Harold Varmus, the Director of NIH, in our audience, who is our in-house Nobel laureate.

Dr. Bishop, we understand that you are going to be our master of ceremonies. I wonder if you would start off by introducing the scientists who are with you this morning and then proceed as you wish.

INTRODUCTION OF PANEL

Dr. BISHOP. Thank you, sir.

Mr. Chairman, Members of the subcommittee, I am Dr. Michael Bishop from the University of California, San Francisco, and with me today are Dr. Michael Brown, University of Texas in Dallas; Dr. David Hubel from the Rockefeller University in New York; and to my right Dr. Joseph Murray from Harvard Medical School, that is in Boston; Dr. Phillip Sharp from the Massachusetts Institute of Technology, which is not in Boston, but in Cambridge; and Dr. James Watson from the Cold Spring Harbor Laboratory on Long Island.

There is prominence in the Northeast among these individuals that is in the interest of economy; it is not due to the distribution of intellectual talent across the land. I am from California.

We are very grateful to be here, I must say that. One distinguished wag has referred to us as a gaggle of Nobel laureates. I can only hope that we will be more coherent than a gaggle of geese.

BUDGETARY CONSTRAINTS

Mr. OBEY. Dr. Bishop, I wonder if I might interrupt for just a second. It is the normal practice for the Chair and the Ranking Democrat to make a statement of welcome. The Chairman just forgot, but I do want to do that and apologize because I have to leave.

The Secretary of the Treasury is in another meeting and he has a lot bigger problems than you have this morning. I would simply like to say before you begin, my staff will be here to listen, that I think it is predictable what you are going to say, and I also think it is predictable that most Members of this committee would like to oblige, given the great respect we have for you and the great support that we feel for the NIH and associated research facilities around the United States.

I just think it is imperative that you understand that you probably have a much bigger problem than you are aware of. If you take a look at what has happened over the past few years, we have had over the last 10 years an increase for health-related R&D from $11 billion to about $30 billion. Between 1985 and 1995, NIH appropriations increased by 114 percent from $5.5 billion to $11.3 billion. The number of grants increased from 19,700 to almost 24,000.

I know that is not quite as rapid a growth as it was in the 1960s, but by the time you see what is in store for everybody in the remainder of the 1990s, it is going to look like the good old days.

So that you understand the squeeze in which you are going to be found, if we have to get to a zero deficit by the year 2002, and if defense is put off limits, and if the tax cut which the Republican leadership is talking about passing, in fact, is passed, that will mean that 31 percent of everything else that we would be doing by the year 2002 would have to be cut. If you exclude Social Security from any cuts, and if you exclude Medicare as well, it means we would have to cut what we are doing by about 42 percent.

To me, that is a prescription for a train wreck, not just in science, but other places. But I think you need to understand that the research that you are testifying about is in great peril, as is a lot of other research in other places, and as are a lot of other programs as well.

I am sorry for interrupting, but I did want to get that on the record, and thank you for being here and apologize for not being able to stay.

Dr. BISHOP. We appreciate your comments.

Mr. PORTER. I would like to apologize to my distinguished Ranking Member. It was certainly a thoughtless oversight on my part, and I do apologize.

Dr. BISHOP. Well, we are only too cognizant of the circumstances you have described, sir. That is why we are here. Our job is to tell you what science has accomplished for the country, and it is your job to decide how to support it. We are going to talk about science today, nonetheless, in large part.

Mr. OBEY. Good luck.

OPENING STATEMENT—DR. MICHAEL BISHOP

Dr. BISHOP. Well, we are here to bear witness to our belief that biomedical research is an investment with rich and inevitable returns, an investment that regularly enhances both the health and the economic welfare of our Nation, an investment that the American people can ill-afford to renounce or even appreciably diminish.

Now, we are going to defend this belief by telling you stories from our own lives as scientists. First and foremost, we want to generally emphasize the benefits of science, but we also want to share with you the grandeur and the excitement of being a scientist, the excitement of science as a human endeavor.

Now my own story concerns cancer. No illness strikes greater fear in the human heart. One person in every four in this room, in this building, in this city, in this land, will develop cancer. One person in every five here will die of that disease, and usually the deaths will involve deep suffering.

When I studied medicine 30 years ago, it seemed to me that we might never fully understand cancer, which takes so many different forms and has so many different causes. I have a student paper still in my files in which I essentially said that. That has all changed. Over the last two decades, we have found our way to what is, in essence, a single, unifying explanation for cancer, an explanation that promises a unified strategy for the conquest of that disease. And that explanation is based on cells and genes.

So let's begin with a brief biology review that will be useful for all of the subsequent talks. Cells, of course, are the microscopic living bricks that compose and run our bodies. There are billions upon billions, to use a familiar phrase, of those cells in each of our bodies, and in order to construct and maintain our bodies, cells have to proliferate. They have to divide, and the magnitude of that division is staggering: every second, 25 million cells divide in our bodies. Every minute, more cells divide in our bodies than there are people in our Nation. And usually, those divisions occur in the right place at the right time, obeying very strict rules. But when the rules are broken, cancer may arise.

What sets the rules? What governs the proliferation of cells and why does that governance fail in cancer? The answer we now know lies in genes. Genes are for me the chemical script for the lives of our cells. A script that is written on that remarkable molecule we know as DNA, whose structure was first deduced by Dr. Watson and his colleague, Francis Crick.

And if my colleague, Michael Brown will flip the poster over for me there, please, I will show you an illustration that captures the essence of the cancer cell.

Of the 40,000 or so genes in each of our cells, only a few hundred are used to govern the proliferation of the cell. Some of these genes serve as accelerators for the engine of cellular growth. In the diagram, these accelerators are called proto-oncogenes.

I apologize for the nomenclature. You can ignore it, although your children cannot. It occurs in most textbooks in high school and college biology.

And the other genes are brakes on cellular growth, and these we happen to call tumor-suppressor genes, and I refer you to the entire of page A–3 in yesterday's Washington Post for a dissertation of that problem. These are not esoteric matters, unless you regard the Washington Post as an esoteric matter—some of you here might. So if you jam an accelerator or if you jam a brake, you have the makings of a relentless cellular proliferation.

So cancer reduces to a single ailment damage to the genetic accelerators and brakes of our cells, damage that scientists would call mutations, damage that creates, literally creates cancer genes within us. Most simply put, chemical damage to DNA is the essence of the cancer cell.

For reasons that are not yet entirely clear, the cell uses many accelerators and many brakes to achieve its purposes. Accordingly, when we examine cancer cells, we usually find that more than one of the accelerators has been jammed and more than one brake has been removed. Cancer is a disease of molecular combinations, accelerators jammed and brakes removed.

It takes time, of course, it is simply a statistical matter that it takes time for this combination to accumulate during the course of our lives, and that we believe accounts for the fact that most cancer is a disease of middle-age and later.

I would like to tell you briefly how the genetic accelerators were found. It is a story that illustrates so well how science is done. It also is, in part, my own story.

In 1911, a scientist named Peyton Rous working at the Rockefeller Institute discovered a virus that causes cancer in chickens. It was the first cancer virus brought fully to view, yet most scientists of the time demeaned the accomplishment. After all, chickens are not interesting outside of Arkansas, perhaps.

Now, half a century later, the virus of Peyton Rous gave rise to a series of discoveries that changed the very face of cancer research. First, scientists learned that the virus itself possesses a cancer gene, a gene that can switch cells from normal to cancerous growth literally overnight. This was the first cancer gene ever sighted in a virus from a chicken.

Then, a team of investigators led by Harold Varmus and myself learned something that seemed to me at least at first almost beyond belief: that cancer gene in the virus of Peyton Rous had been captured from a normal cell, in an accident of nature that no one could have anticipated. Moreover, the same gene is found in many creatures, essentially all multicellular organisms, including human beings.

Here then was a potential cancer gene lurking in our own DNA, although first found in a cancer virus of chickens. Soon it became clear that there are many such genes. We now know of more than

100. So these are the accelerators, the proto-oncogenes of which I spoke before.

In their normal guise, they are vital to our cells. They are essential to the control of cellular proliferation. But when damaged, they become outlaws, jammed accelerators that drive a cell to cancerous growth. By now we can point to at least one jammed accelerator in essentially every form of human cancer, and we have no doubt that they are a universal feature of cancer.

So we have a powerful new view of cancer achieved only in the last 5 to 10 years. The seemingly countless causes of cancer—asbestos, cigarette smoke, sunlight, chemicals, viruses, and many others, many not yet known—all of these work in a single way: by playing on a genetic keyboard, by damaging a few of the genes in our DNA, by jamming the accelerators and removing the brakes of our cells. An enemy has been found, and we are beginning to understand its lines of attack. And it all began with a chicken virus.

Now, what does this new view promise for our ability to fight cancer? Briefly put, it is going to change every aspect of our strategies against cancer; it is going to tell us new things about the causes of cancer, and thus, open up new approaches to prevention; it will allow earlier detection of cancer cells in our bodies, it already is, and earlier detection usually means a better chance at cure; it will allow us to refocus our therapeutic strategies in ways that we could not have imagined, could not have dreamed of 10 years ago.

There are even benefits beyond the realm of cancer. I would like to name just one, because it plays into what you are going to hear from Dr. Brown. Cardiovascular disease. Every year, tens of thousands of Americans have obstructions removed from the blood vessels of their hearts in order to relieve the pain of angina pectoris and reduce the threat of heart attacks. But in almost half of these instances, the obstructions quickly return, due to the proliferation of cells that surround the blood vessels and constrict them.

Medical scientists have now realized that by manipulating the cellular accelerators, the genetic accelerators and the genetic brakes first discovered through the study of cancer cells, it may be possible to prevent the recurrence of obstructions. If successful, this tactic will represent a benefit of cancer research in cardiovascular disease that no one would have predicted.

So having heard my story, perhaps you can understand why for the first time in my 30 years as a biomedical scientist and for the first time in a public setting, I say that I now believe that we will conquer cancer. It may take several generations more of hard work, but the strategies for conquest are now clear; we need only work out the tactics.

So that is the question that remains: can we muster the resources for the conquest? And that is a question only you and your colleagues on this Hill can answer.

But I want to close with a comment about one of those resources, the resource which I consider most vital and most endangered, the next generation of scientists, just now taking form in our Nation's schools and laboratories. These young people have not missed the view that our Nation is insolvent and may not be able to sustain biomedical research as it has in the past. That message has been sent to them in many different forms, not only in the musings of this subcommittee. And they can see only one sensible response: get out of science, find something else to do.

My own son has done just that, halfway through his preparation to be a physicist. I can think of few losses that could be more damaging to our Nation's future.

I have just returned from Israel where I happened to visit the grave of Chaim Weizmann, the distinguished chemist who became the first President of Israel. In 1946, while Israel was still struggling to find its identity as a Nation, Weizmann founded an institute for fundamental research that now bears his name in Rehovot, Israel.

It must have seemed irrational, the records show that it did seem irrational to many observers that a nation still on the brink of survival would devote precious resources to a research institute. But Weizmann had his reason, and it is inscribed on the memorial at his grave. Here is that inscription: I feel sure that science will bring to this land both peace and a renewal of its youth—creating here the springs of a new spiritual and material life. And to this day, that is the way the Israelis I know look to the Weizmann Institute.

As you and your colleagues in Congress wrestle with the future of biomedical research in the United States, keep in mind that there is more at stake than balance sheets. Keep in mind that at stake is one of the most nourishing springs for our Nation's spiritual and material life.

Thank you very much, sir.

[The prepared statement of Dr. Michael Bishop follows:]

Mr. Chairman and Members of the Subcommittee:

Let me first introduce myself and my colleagues to you.

I am Dr. Michael Bishop, from the University of California, San Francisco. With me are Dr. Michael Brown, from the University of Texas in Dallas, Dr. David Hubel from the Rockefeller University in New York, Dr. Joseph Murray from Harvard Medical School in Boston, Dr. Phillip Sharp from the Massachusetts Institutes of Technology in Cambridge, and Dr. James Watson from the Cold Spring Harbor Laboratory on Long Island.

We are grateful for the privilege to appear before you. We are all biomedical scientists who have been fortunate to receive the Nobel Prize for our work. We are here to bear witness to our belief that biomedical research is an investment with rich and inevitable returns, an investment that regularly enhances both the health and the economic welfare of our nation, an investment that the American people can ill afford to renounce or even diminish.

We will defend this belief by telling you stories from our lives as scientists. First and foremost, we want to illustrate the benefits of science. But we hope also to show you the grandeur and excitement of science as a human endeavor. In short, we are here to teach.

My own story concerns cancer. No illness strikes greater fear in the human heart. One person in four in this room will develop cancer, one in five will die of the disease - and those deaths will usually involve deep suffering.

When I studied medicine thirty years ago, it seemed to me that we might never fully understand cancer, which takes so many forms and has so many causes. Now all that has changed. Over the past two decades, we have found our way to a single explanation for all cancer, an explanation that promises a unified strategy for the conquest of this daunting enemy. The explanation is based on cells and genes.

Cells are the microscopic living bricks with which our bodies are built - billions upon billions of them in each of us. In order to construct and maintain our bodies, cells must proliferate. The magnitude of that proliferation is staggering: every second, in each of our bodies, twenty-five million cells divide to become fifty million. Usually, those divisions occur in the right place and at the right time, obeying strict rules. But when the rules are broken, cancer may arise.

What sets the rules? What governs the proliferation of cells and why does that governance fail in cancer? The answer lies in genes. Genes are the chemical script for the lives of all our cells, a script that is written on that amazing molecule known as DNA - whose structure was first deduced by Dr. Watson and his colleague, Francis Crick.

Some genes serve as accelerators for the engine of cellular growth. In the diagram, these accelerators are called proto-oncogenes. Other genes serve as brakes on cellular growth: these we call tumor suppressor genes. Jam an accelerator or remove a brake, and you have the makings of relentless cellular proliferation - the root of cancer. So cancer reduces to a single ailment: damage to the genetic accelerators and brakes of our cells, damage that scientists call "mutations", damage that creates cancer genes within us.

For reasons that are not yet entirely clear, the cell uses many accelerators and many brakes to achieve its purposes. Accordingly, when we examine cancer cells, we usually find that more than one of these genes is damaged: cancer is a disease of molecular combinations - accelerators jammed and brakes removed. It takes time for these combinations to accumulate during the course of our lives and, thus, most cancer is a disease of middle age or later.

I want to tell you briefly how the genetic accelerators were found. It is a story that illustrates so well the way in which science proceeds. And it is in part my own story.

In 1911, a scientist named Peyton Rous at the Rockefeller Institute discovered a virus that causes cancer in chickens. It was the first cancer virus ever discovered, yet most scientists of the time demeaned the discovery. After all, chickens are not interesting.

Half a century later, however, the virus of Peyton Rous gave rise to a series of discoveries that changed the face of cancer research. First, scientists learned that the virus itself possesses a gene that can single-handedly switch cells from normal to cancerous growth. This was the first cancer gene ever sighted.

Then, a team of investigators directed by Harold Varmus and myself learned something that at first seemed almost beyond belief: the cancer gene in the virus of Peyton Rous had been captured from a normal cell, in an accident of nature that no one could have anticipated. Moreover, the same gene could be found in many different creatures, including human beings. Here then was a potential cancer gene, lurking in our DNA. Soon it became clear that there are also many other such genes in our cells - we now know of more than one-hundred.

These genes are the accelerators - the proto-oncogenes - of which I spoke before. In their normal guise, they have vital roles in the governance of our cells. But when damaged, they can become outlaws - jammed accelerators that cause cells to run amok. By now, we can point to at least one jammed accelerator in almost every form of human cancer. We have no doubt that they are a universal feature of cancer.

I have no time to tell you the story of how the genetic brakes were found. But I assure you that it is equally astonishing.

So we have a powerful new view of cancer. The seemingly countless causes of cancer - cigarette smoke, sunlight, asbestos, chemicals, viruses, and many others - all these may work in a single way, by playing on a genetic keyboard, by damaging a few of the genes in our DNA, by jamming the accelerators and removing the brakes of our cells. An enemy has been found, and we are beginning to understand its lines of attack. And it all began with a chicken virus.

What does this new view promise for our ability to fight cancer? Simply put, it is going to change every aspect of our strategies against cancer:

- it will eventually tell us new things about the causes of cancer, and thus open up new approaches to prevention;
- it will allow earlier detection of cancer cells in our bodies, and earlier detection usually means a better chance for cure;
- and it will allow us to refocus our therapeutic strategies in ways that we could not even have imagined ten years ago.

There are benefits even beyond the realm of cancer. Consider cardiovascular disease. Every year, tens of thousands of Americans have obstructions cleared from the blood vessels of their hearts, in order to avoid the pain of angina pectoris and the threat of heart attacks. But in almost half of these instances, the obstructions quickly return, in the form of proliferating cells that surround the blood vessels. Medical scientists are now trying to manipulate the genetic accelerators and brakes of cells in an effort to prevent the reobstruction. If successful, the tactic would represent a benefit of cancer research that no one could have predicted ten years ago.

Having heard my story, perhaps you can understand why - for the first time in my thirty years as a biomedical scientist - I now believe that we will eventually conquer cancer. It may take several generations more of hard work, but the strategies for conquest are clear.

Can we muster the resources for conquest? That is a question only you and your colleagues here on this hill can answer. But I want to close with a comment about one of those resources - the resource which I consider most vital - the next generation of scientists, just now taking form in our nation's schools and laboratories.

These young people have heard the view that our nation is "insolvent" and may not be able to sustain biomedical research as it has in the past: the message has been sent to them in many different forms, not just through the musings of this committee. They can see only one sensible response: get out of science, find something else to do. I can think of few losses that would be more damaging.

I have just returned from Israel, where I happened to visit the grave of Chaim Weizmann - the distinguished chemist who became the first president of Israel. In 1946, while Israel was still struggling toward identity as a nation, Weizmann founded the institute for fundamental research that now bears his name in Rehovot, Israel.

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I appeal to you. As you wrestle with the future of biomedical research in the United States, keep in mind that there is more at stake than balance sheets. Keep in mind that at stake is one of the most nourishing springs for our nation's spiritual and material life.

Dr. BISHOP. I gather you would like us to proceed in order.

So you will hear next from Dr. Brown, whom I have already introduced to you from the University of Texas in Dallas.

OPENING STATEMENT—DR. MICHAEL BROWN

Dr. BROWN. Thank you.

Mr. Chairman, Members of the subcommittee and guests, despite my deference to Michael Bishop and his concern about cancer, we must realize that the most frequent cause of death in the United States is atherosclerosis, which laymen call hardening of the arteries. This disease causes more than 40 percent of all deaths.

Its most common manifestation, heart attack, kills more than 500,000 Americans every year. The disease is the most frequent cause of death among women, as it is among men, and it affects all racial and ethnic groups. I believe that atherosclerosis will one day be a disease of the past, like polio and smallpox. To help you understand this optimism, let me tell you about the disease process itself and what we have learned over the years.

First of all, atherosclerosis is a chronic progressive disease. It begins in the teenage years when cholesterol begins to deposit in the walls of arteries like sludge on a boiler pipe. In response, the artery wall thickens and the channel narrows. Eventually, a blood clot forms and the tissue supplied by that artery dies. When this happens in the brain, we call it a stroke. When it happens in the heart, we call it a heart attack.

The cholesterol that deposits in the artery wall comes from the bloodstream. All of our cells require cholesterol for normal health. It is part of the cell wall that surrounds all the billions of cells that Mike Bishop described. So the liver secretes cholesterol into the blood stream in order to carry it to all of the cells, and it is carried in microscopic particles which are called lipoproteins.

Blood contains several different kinds of lipoproteins, but the most dangerous is low density lipoproteins or LDL. LDL is what laymen refer to as bad cholesterol, because LDL has a tendency to stick to the artery wall and deposit its cholesterol, forming in sludge. The higher the concentration of LDL in the blood, the more rapidly atherosclerosis occurs. On the other hand, when LDL is low, atherosclerosis is extremely rare.

Now, LDL isn't the only factor that contributes to atherosclerosis, but it is clearly the most important cause. Other risk factors like cigarette smoking, high blood pressure, and diabetes accelerate the disease, but these factors are only dangerous when the level of cholesterol in the blood is high. When the level of cholesterol is very low, even cigarette smoking and high blood pressure and diabetes don't produce heart attacks.

In the United States, the average cholesterol level in blood is about 210 milligrams percent. This is high enough to allow cigarettes and blood pressure to accelerate coronary artery disease. But in rural Japan and China where the level of cholesterol in the blood is below 160 milligrams percent, heart attacks are rare, even though smoking and high blood pressure are common.

What controls the level of cholesterol in blood and why do 40 percent of Americans have an LDL level that is high enough to kill them? My colleague, Joe Goldstein, and I set out more than 20 years ago to answer that question. Both of us had been trained as physicians. We had also learned basic science at the National Institutes of Health in Bethesda, Maryland. In 1973 we established a laboratory in Dallas to apply the emerging science of cell biology and molecular biology to the study of atherosclerosis.

We discovered that the level of LDL in blood is controlled by a protein called the LDL receptor. The LDL receptor is produced by cells in the body and it sits on the surface of cells facing into the bloodstream, and its job is to remove LDL from blood. The receptor has a structure that allows it to bind the LDL particle, like a first base man reaching out to catch a ball thrown by a shortstop when they used to play baseball in this country.

Once the receptor catches the LDL, it carries it into the cell, and the cell destroys the LDL and releases the cholesterol so that the cell can release the cholesterol to build its wall. Now, if a person has a large number of LDL receptors, then LDL is quickly removed from the blood and the level of LDL is very low. On the other hand, if something happens to reduce the LDL receptors, then LDL is removed slowly from blood, it builds up in the plasma, and we see heart attacks.

Now, there are several causes of deficiency of LDL receptors. One of these is a genetic disease called familial hypercholesterolemia or FH, which affects 1 in over 500 people in the United States. It is the most common single gene disease that causes symptoms, and it cuts across all ethnic and racial groups in the world.

So 1 in over 500 people throughout the world has this genetic defect. And these people have a mutation in the gene that produces the LDL receptor. So they are unable to remove LDL from blood at normal rates, and their LDL levels are very high from the moment they are born. And 80 percent of these people will eventually die of heart attacks, usually in the fifth and sixth decades of life.

So FH in itself is a very important disease. It affects about 400,000 Americans. But 80 million Americans have high levels of LDL in blood. The vast majority of these people have normal LDL receptor genes. Why is the LDL level so high among people with normal LDL receptor genes?

Well, the answer we now know is the amount of cholesterol in the diet. When humans consume a diet that is rich in cholesterol and animal fats, the level of LDL in blood rises. This occurs because the cholesterol that we eat enters the liver and it causes the liver to produce more lipoproteins and at the same time, it reduces the production of LDL receptors. So the combination of an increased LDL secretion and a decreased removal rate leads to a very high LDL level when people eat cholesterol.

Well, now, let me give you the good news. The good news is that atherosclerosis can be prevented. The vast majority of heart attacks can be avoided, and this can be done by two methods. The first is the diet. When we consume a strict low-fat, low-cholesterol diet, the plasma cholesterol usually drops below the threshold for atherosclerosis. The problem with this approach is that it requires a very strict diet. To be fully effective, we must almost eliminate the intake of meat and dairy products. Most people find it impossible to follow such a strict diet. There seems to be an inborn craving for high-fat foods, which is easily satisfied in our society.

And this is where the second preventive treatment comes in: the use of cholesterol-lowering drugs. Eight years ago, a new class of drugs was introduced to the world. These drugs are potent in reducing LDL cholesterol levels, and they have a remarkably low incidence of side effects. The drugs, called HMG CoA reductase inhibitors, block cholesterol production in the body.

Now, to understand how they work, you have to realize that the human liver produces cholesterol, even though we take in large amounts in the diet. And these reductase inhibitors slow the production of cholesterol. The liver produces fewer LDL particles and the number of receptors increases. So the combination of reduced production and enhanced removal leads to a drop. These drugs, the HMG CoA reductase inhibitors, can lower LDL by up to 50 percent, which is sufficient to rescue many people from the danger zone for heart attacks.

The first HMG CoA reductase inhibitor goes by the trade name of Mevacor and it was developed by Merck, Sharp and Dohme in New Jersey. The drug was a product of rational drug design based on fundamental knowledge that had been gathered over the previous two decades, largely in university laboratories.

The Merck scientist set up a biomedical screening assay to detect agents that would block the production of cholesterol and increase LDL receptors, and the result was the first potent cholesterol-lowering agent. Three related drugs were subsequently introduced into the United States. One of them called Zocor is also manufactured by Merck, and others are manufactured by Bristol Myers Squibb and by Sandoz.

The power of these drugs to lower cholesterol was immediately recognized by the medical community. Even though they have only been available for eight years, there are more than 3 million people taking these drugs throughout the world.

Several studies showed that Mevacor and its relatives can halt the production of atherosclerosis and, in some cases, they can actually shrink atherosclerotic plaques. They show that people taking Mevacor have a reduction in heart attacks.

But the really important question remained unanswered until just a few months ago, and that question was does cholesterol lowering actually save lives? Because up to this point, although we knew that lowering cholesterol reduced heart attacks, nobody had a drug that was potent enough to lower cholesterol sufficiently to actually extend life-span.

But that question was answered in the affirmative three months ago with the publication of a large clinical study that was conducted in Scandinavia, it is called the 4S study. The study involved more than 4,000 patients who already had coronary heart disease. Most of them had already had a heart attack.

The patients were divided into two groups; one group was given the cholesterol-lowering drug Zocor, one of these reductase inhibitors, and the other group received a placebo control. The patients were followed for five-and-a-half years. The results showed that the treated patients had a remarkable 42 percent decrease in deaths from coronary heart disease. But even more important, there was a 30 percent reduction in total mortality. That is, at the end of five years, 30 percent of the patients who would otherwise have died from all causes, were still alive and in better health. There was also a decrease in hospitalizations for heart attacks as well as bypass surgery and balloon angioplasty.

As dramatic as these results are, we believe they underestimate the true benefits of cholesterol-lowering therapy. Remember that the treated patients already had severe coronary heart disease. Their blood vessels were already narrowed. Even so, there was a 42 percent reduction in the coronary death rate.

We believe that the reduction will be much higher when the patients are treated before they develop coronary heart disease. It should be much easier to prevent the growth of the atherosclerotic plaque than it is to reverse the plaque. Attaining this goal will require preventive therapy.

We must treat patients before they show clinical signs of heart disease. But the big question then becomes who to treat. The 4S study used patients who had known coronary heart disease, but how do we detect this disease before heart attacks occur?

One way is through measurement of the cholesterol level itself. Experience shows that people with cholesterol levels above 240 are at increased risk for heart attacks, and we believe that these people should definitely take measures to lower their cholesterol with diet and if necessary, cholesterol-lowering drugs.

But a more difficult question relates to people with cholesterol levels between 200 and 240. These individuals constitute the majority in our society. They are at significant risk for heart attack, but the risk isn't so high that it justifies treating everyone.

Well, this is where the other risk factors come in. People with these moderately high cholesterol levels should be treated with cholesterol-lowering drugs if they are resistant to dietary therapy and if they have other risk factors such as high blood pressure, cigarette smoking, diabetes or a family history of premature coronary artery disease. We believe that if this policy is followed, a major reduction in the incidence of heart attacks with all of the personal suffering and the cost to individuals and society will be avoided.

Now, let me just briefly review what I have said. Atherosclerosis causes 40 percent of all deaths in the United States. The major risk factor is elevated cholesterol. Through basic science, we have learned to control the level of cholesterol in the blood. We know that we can reduce the number of heart attacks and increase the life-span of patients who have coronary disease, and we believe that if we apply these principles on a large population scale, we could have a major reduction in the major killer of Americans.

All of this progress can be attributed directly to basic science research that has been supported for the last 40 years by the United States National Institutes of Health. It is an accomplishment for which the United States people and its government are entitled to justifiable pride.

Thank you.

[The prepared statement of Dr. Michael Brown follows:]

Congressional Testimony, February 28, 1995
Michael S. Brown, M.D., Professor of Medicine and Molecular Genetics
University of Texas Southwestern Medical Center, Dallas, Texas

MR. CHAIRMAN, MEMBERS OF THE SUBCOMMITTEE, AND GUESTS:

The most frequent cause of death in the United States is atherosclerosis, which laymen call "hardening of the arteries." This disease causes more than 40% of all deaths. Its most common manifestation, heart attack, kills more than 500,000 Americans every year. The disease is the most frequent cause of death among women as it is among men, and it affects all racial and ethnic groups. I believe that atherosclerosis will one day be a disease of the past like polio and smallpox. To help you understand this optimism let me tell you about the disease process.

Atherosclerosis is a chronic progressive disease. It begins in the teenage years when cholesterol deposits in the walls of arteries like sludge on a boiler pipe. In response, the artery wall thickens and the channel narrows. Eventually, a blood clot forms and the tissue supplied by that artery dies. When this happens in the brain, we call it a stroke. When it happens in the heart, we call it a heart attack.

The cholesterol that deposits in the arteries comes from the bloodstream. All of our cells require cholesterol for their normal health. The liver secretes cholesterol into the blood in microscopic particles called lipoproteins. Blood contains several different kinds of lipoproteins, but the most dangerous is low density lipoprotein or LDL. Laymen refer to LDL as "bad cholesterol" because of its tendency to stick to the blood vessel wall. The higher the concentration of LDL in blood, the more rapid the atherosclerotic process. Conversely, when LDL is low, atherosclerosis is rare.

LDL is not the only factor that contributes to atherosclerosis, but it is the most important cause. Other risk factors such as cigarette smoking, high blood pressure, and diabetes accelerate the disease. But these factors are only dangerous when the level of cholesterol in the blood is high. When the level of cholesterol in blood is very low, cigarette smoking, high blood pressure and diabetes do not produce heart attacks. In the United States the average cholesterol level in blood is about 210 mg %. This is high enough to allow cigarettes and high blood pressure to accelerate coronary artery disease. In rural Japan and China where the level of cholesterol in the blood is below 160 mg %, heart attacks are rare even though smoking and high blood pressure are common.

What controls the level of LDL in blood? And why do 40% of Americans have an LDL level that is high enough to kill them? My colleague, Joe Goldstein and I set out more than 20 years ago to answer that question. Both of us had been trained as physicians. We had also learned basic science at the National Institutes of Health in Bethesda, Maryland. In 1973 we established a laboratory in Dallas to apply the emerging science of cell biology and molecular biology to the study of atherosclerosis.

We discovered that the level of LDL in blood is controlled by a protein called the LDL receptor. The LDL receptor is produced by cells in the body and it sits on the surface of the cells facing into the bloodstream where its job is to remove LDL from blood. The receptor has a three-dimensional structure that allows it to bind the LDL particle. The bound LDL is taken into the cells and is destroyed completely. The cholesterol of LDL is liberated within the cell and is used by the cell for necessary metabolic purposes.

If an individual has a large number of LDL receptors, LDL is quickly removed from blood and the level of LDL is very low. On the other hand, if LDL receptors are reduced, LDL particles are removed slowly from blood and they accumulate to high levels eventually depositing in the arteries.

There are several causes of LDL receptor deficiency. One of these is a genetic disease called familial hypercholesterolemia or FH which affects 1 in every 500 people in the United States. FH patients have a mutation in the gene for the LDL receptor. They are unable to remove LDL from the blood at normal rates, and therefore, they have high LDL levels from the day that they are born. More than 80% of affected individuals will eventually die of heart attacks, usually in the fifth and sixth decades of life.

FH affects about 400,000 Americans. Yet, 80 million Americans have high levels of LDL in the blood. The vast majority of these people have normal LDL receptors. Why are their LDL levels so high?

The answer for most people is the amount of cholesterol is the diet. When humans consume a diet that is rich in cholesterol and animal fats, the level of LDL in blood rises. The cholesterol in the diet enters the liver and it increases the amount of cholesterol secreted in LDL. At the same time, the cholesterol reduces the production of LDL receptors. Elevated LDL secretion and decreased LDL receptors leads to a rise in the level of LDL in blood.

Now let me give you the good news. The good news is that atherosclerosis can be prevented. The vast majority of heart attacks can be avoided. This can be done by two methods. The first is the diet. When people consume a strict low-fat, low-cholesterol diet, the plasma cholesterol level usually drops below the threshold for atherosclerosis. The problem with this approach is the very strict diet. To be fully effective, we must restrict the intake of meat and all dairy products. Most people find it impossible to follow such a strict diet. They have an inborn craving for high fat foods, which is easily satisfied by all of the available foods.

This is where the second preventive treatment comes in: the use of cholesterol lowering drugs. Eight years ago, a new class of drugs was introduced to the world. These drugs are potent in reducing LDL cholesterol levels and they have a remarkably low incidence of side effects. The drugs, called HMG CoA reductase inhibitors, block cholesterol production in the body. To understand how they work, we must understand that the human liver produces cholesterol, even when we take in large amounts of cholesterol in the diet. The HMG CoA reductase inhibitors slow the production of cholesterol. The liver produces fewer LDL particles, and the number of LDL receptors increases. The combination of reduced production and enhanced removal leads to a profound drop in plasma LDL levels. The HMG CoA reductase inhibitors can lower plasma LDL by up to 50%, which is sufficient to rescue many people from the danger zone for heart attacks.

The first HMG CoA reductase inhibitor goes by the trade name of Mevacor. It was developed by Merck, Sharp, and Dohme in New Jersey. The drug was a product of rational drug design based on fundamental knowledge that had been gathered over the previous two decades.

The Merck scientists set up a biochemical screening assay to detect agents that would block the production of cholesterol and increase the production of LDL receptors. The result was Mevacor, the first potent cholesterol lowering agent. Three related drugs were subsequently introduced into the U.S. market. One of them, called Zocor, is also manufactured by Merck. Others are manufactured by Bristol Myers Squibb and by Sandoz.

The power of these drugs to lower plasma cholesterol was immediately recognized by the medical community. Drugs in this class are now taken daily by more than 3 million people throughout the world.

Several studies have shown that Mevacor and its relatives can halt the progression of atherosclerosis and in some cases, they can actually shrink atherosclerotic plaques. These studies also showed that patients taking Mevacor have a reduction in heart attacks. But the really important question remained unanswered until a few months ago. That question was: does cholesterol lowering actually save lives? That question was answered in the affirmative three months ago with the publication of a large clinical study conducted in Scandinavia, the 4S study. The study involved more than 4,000 patients who already had coronary heart disease. Most of them had already experienced at least one heart attack. The patients were divided into two groups. One group was given the cholesterol lowering drug Zocor, and the other group received a placebo control. The patients were followed for at least five years. The results showed that the treated patients had a remarkable 42% decrease in deaths from coronary heart disease. But even more important, there was a 30% reduction in total mortality. That is, at the end of five years, 30% of the patients who would otherwise have died were still alive and in better health. There was also a decrease in hospitalizations for heart attack as well as coronary by-pass surgery and balloon angioplasty.

As dramatic as the 4S results are, we believe that they underestimate the true benefits of cholesterol reducing therapy. Recall that the treated patients already had severe coronary heart disease. Their blood vessels were already narrowed by cholesterol deposits. Even so, there was a 42% reduction in the coronary death rate. We believe that the reduction will be much higher when the patients are treated before they develop coronary heart disease. It should be much easier to prevent the growth of the atherosclerotic plaque than it is to reverse that plaque once it has developed. Attaining this goal will require preventive therapy. We must treat patients before they show clinical signs of heart disease.

In preventive therapy the big question is, who to treat? The 4S study used patients who had known coronary disease. But how do we detect this disease before heart attacks occur? One way is through measurement of the cholesterol level itself. Experience shows that people with cholesterol levels above 240 mg % are at increased risk for heart attacks and we believe that these people should take measures to lower their cholesterol level. The first step is diet, but if this doesn't work many of these people should be treated with cholesterol lowering drugs. A more difficult question relates to people with cholesterol levels between 200 and 240 mg %. These individuals constitute the majority in our society. They are at significant risk for heart attack, but the risk is not so high that it justifies treating everyone. This is where the other risk factors come in. People with these moderately high cholesterol levels should be treated with cholesterol lowering agents if they are resistant to dietary therapy and if they have other risk factors such as high blood pressure, cigarette smoking, diabetes, or a family history of premature coronary artery disease.

Let me review what I have said. Atherosclerosis causes 40% of all deaths in the United States. The major risk factor is an elevated level of LDL cholesterol. Through basic science, we have learned to control the level of LDL cholesterol in the blood. This therapy reduces the number of heart attacks and increases the lifespan of patients who already have coronary artery disease. We believe that these principles if applied on a large population scale could lead to a major reduction in the major killer of Americans. All of this progress can be attributed directly to basic science research that has been supported for the last 40 years by the United States National Institutes of Health. It is an accomplishment for which the United States people and its government are entitled to justifiable pride. Thank you.

B3/165

Dr. BISHOP. Our next speaker will be Dr. David Hubel.

In mentioning Dr. Hubel, before I committed what is perhaps one of worst conceivable sins for a scientist, I identified a Harvard professor as coming from Rockefeller.

Dr. HUBEL. Well, thank you, Mr. Chairman and Members of the subcommittee. I don't quite know whether to feel insulted or complimented.

Dr. BISHOP. We will advise you later, David.

OPENING STATEMENT—DR. DAVID HUBEL

Dr. HUBEL. I work on the brain. And by that, what I mean is that I put small wires into the brains of animals—because we, obviously, can't do this in humans—and record the nerve impulses and ask what happens in the brain during behavior when we remember, when we plan, when we perceive, and everything, in fact, that we do. One has to start somewhere, and I happen to work on the visual part of the brain because it is the most approachable perhaps of all subcategories of brain function.

As I say, we do the work in animals.

I started out in the early 1950s in Montreal, where I trained as a neurologist, and then went to the USA. My parents were American, so that was the natural thing to do. But I was immediately drafted into the Doctors' Draft, and with a terrific streak of luck I went to Walter Reed Army Institute of Research, and there I got started in research.

I had never done a tad of research until then, and starting out was given complete freedom to do anything I wanted, providing it involved neurobiology, neurophysiology, which is, in fact, what I wanted to do. And I groped around for some time trying to hit on a topic, decided in the end that I would take something which would have only been thought of at the time as risky, that is the project of trying to record from single cells in the brain, which only a very few people had succeeded in doing, and more than that, the brains of animals that were awake, cats that were purring, behaving, that hadn't been done by anyone.

I chose the visual part of the brain to work on, as I say, partly by accident, partly because it seemed to be the most easily approachable.

By the time the three years had gone by, the whole thing had somewhat to my surprise been very successful. I was getting excellent records, and I was beginning to learn something about what the cerebral cortex of the brain did. This was simply terra incognita until then. I don't think anybody had identified anything that was different between what entered the cerebral cortex and what left. And in the visual part, it is perfectly easy now to recognize what this region contributes to our livelihood. It is, in fact, the best known, understood, single part of the central nervous system.

I went from Walter Reed to Johns Hopkins, where I teamed up with Torsten Weisel, in what was to prove to be a 25-year collaboration. He is now President of the Rockefeller Institute, and I am still a humble Professor at Harvard Medical School. But anyhow, all of this work led to our getting the Nobel Prize in 1981.

So by about 1963, after just a few years, we thought that we had come to enough understanding of how this part of the cerebral cortex worked to do some experiments, asking what happens when it goes wrong. And having been trained as clinicians, both of us, we took as a project to look at two conditions that are important in clinical ophthalmology.

What occurs when a child is born with cataracts? It is well-known that if you leave a child for 5 or 10 years with cataracts, then remove the cataracts, which is just an opalescence of the lenses, you remove the cataracts, replace them by a normal—via an implant or by glasses, so that you get a focused image on the retina, you would expect that the child would be able to see. And far from that, the children in whom you do this are blind, and they stay blind. That is blind in the sense that after years of training, they still can't tell a circle from a triangle by visual inspection.

So we asked the question, what would happen if you did the same thing in an animal? So we brought up animals for a few weeks to a month or so, newborn cats and then monkeys, by fitting them with contact lenses that were opalescent in the same way that cataracts are, that is preventing a focused image from falling on the retina.

And after this few weeks or months, we did our usual experiments recording from cells in the brain to ask whether they worked normally or not. And, in fact, the records showed very clearly that there was a massive disruption of the connections. Either the connections from the eye to the brain or the connections within the brain. It was easy to establish that nothing was wrong in the eye, but the trouble actually had occurred in the cerebral cortex, in the first visual area that we had been working on all this time.

If you do the same thing in an adult animal, there are no ill effects at all, and that of course is exactly what you see in humans with cataracts. A man or woman of 60 years of age can have cataracts for several years and not be able to see a thing during that time. You replace the lenses and immediately they see. The same evidently was not true in very young animals. So there is something different about the brains in young animals. It is more susceptible to this sort of insult.

We did another set of experiments looking at animals with cross-eye. It is known that in humans, if you are cross-eyed from a very early age, you have a high chance of becoming blind in one eye. In fact, it is the most important, or certainly one of the most important single causes of blindness in this country. That too, if you do that in an animal, you get similar results as far as vision is concerned, and you can again show a massive change in the connections within the brain that have to do with the eye that has become defective. And again, this occurs early in life and not later on.

Now, the payoff here was that it led to the possibility of correcting both of these conditions. One simply had to persuade the ophthalmologist to do the operation as soon as the condition was recognized. So now the blindness that comes from cross-eyedness and congenital cataracts can be, in most cases, completely avoided simply by doing the operation early. So this, this discovery, if you like, has paid off many, many times since it was made in the mid-1960s.

I should emphasize that we had no idea when we started out studying the brain that it would lead to the ability to forestall any kind of blindness. We were motivated by curiosity. After all, the brain is the most complicated thing in the universe, as far as we know, and it is a marvelous thing to study. It has the same fascination to us as the universe has to the astronomer. And that was one of our main motivations.

Of course, we were motivated by the many important diseases. We don't have one single disease like atherosclerosis or cancer to talk about, but we can talk about things like Parkinsonism, mental retardation, cerebral palsy and a whole list of most important conditions. But in order to address these, you have to know something about how the brain works.

And what has happened in the last 30 or 40 years has been an absolute revolution in that area. One could not record from a single cell in the brain before that time. And now one can.

The period of my work has coincided almost exactly with the tremendous growth and improvement in the support for this sort of research in this country. And, in fact, when we started out in the mid-1950s, you would have to say that in understanding the brain, the leading country was probably England. The United States wasn't far behind, but it certainly didn't come up to the major, major contributions that were being made in England at that time.

Now, the contributions of the USA exceed all of the other countries in the world put together in this area. So it has been an immense success story. It is not that we are on top of the diseases that concern us most, things like developmental problems, mental retardation and all the rest, some of which I have mentioned. This still lies in the future. One thing we can say for sure is that we will never get to the bottom of these diseases unless we keep on studying how the brain works, and we have to start with the normal brain and proceed to the abnormal.

So in the past 10 years, there has certainly been a change in the whole atmosphere of support for this kind of research—as is so with biological research and medical research in general.

Nowadays, if a young person applies for a grant, the chances are 80 percent that it won't be funded. And these aren't just people from unknown places with mediocre training, perhaps. These are people with the best training in the country, it is still a lottery as to whether you get a grant funded or not. And huge amounts of time of young people are consumed in just writing grant requests, because when so much is at stake, a whole career is at stake, you can't afford not to take something like four months of the year in writing requests to get such grants.

So I recognize what has been mentioned already by Representative Obey that the future looks dark. The present is not all that bright, and the major feather in the cap in this country in biology is the support that this sort of work has gotten from the NIH. What we need is well-trained people, time, and steady support, and one certainly hopes that this keeps on.

Thank you.

[The prepared statement of Dr. David Hubel follows:]

Mr. Chairman and Members of the Subcommittee:

For the past 40 years my main interest has been to understand the workings of the brain : how brain cells behave when we think, act, perceive, learn and remember. My work consists of recording electrical impulses from single cells in the brain, by inserting tiny wires that are connected to amplifiers, oscilloscopes and computers. Since one cannot record from brain cells in humans, almost all of my research has been done in cats and monkeys.

I began in 1954, while in the Army at the Walter Reed Army Institute of Research. I had already completed my general medical and neurology training at McGill University but I had had no training in research. Walter Reed was a wonderful place to begin: I could choose my own project, was surrounded by experienced colleagues, and I did not have to write any grant proposals. After some groping I decided to work on the part of the cerebral cortex involved in vision, asking how single nerve cells in the brain react when an animal looks at objects. Only a few people had ever recorded from single cells in the cortex, and no one had studied the visual areas. The choice must have been a good one: the subject is still far from exhausted forty years later, and today hundreds of people are working on it. From the Army, I went to Johns Hopkins Hospital and, a year later, to Harvard Medical School. At Hopkins, I teamed up with Torsten Wiesel, in a collaboration that lasted over 20 years and led to our winning the Nobel Prize in 1981.

One of the first things we learned was that cells in the cerebral cortex react to visual stimuli in a very selective way. A typical cell fires impulses only when an image of a line or edge boundary falls on a particular tiny region of the retina, and then only when the line has a certain orientation, say vertical, has a certain color such as red, and moves in a particular direction such as left-to- right. Much of our efforts have been devoted to unraveling the circuits responsible for this very specialized and specific behavior. Today the visual area of the cortex is by far the best understood of all brain regions. Many other areas of cortex, probably hundreds, are still unexplored, but there is no reason to think that they will not also someday be understood. What we learned in animals almost certainly applies to our own brains, because this part of the cortex is almost identical to the homologous area in humans.

By about 1963, we realized that what we had learned about cells in the normal brains of animals allowed us to ask questions about abnormal vision. It was common clinical knowledge that children born with cataracts (clouded lenses that pass light but smear out retinal images) are still for all intents and purposes blind when a few years later the lenses are surgically removed and replaced with glasses. We decided to raise cats and monkeys from birth with their eyes covered with opalescent contact lenses that acted like cataracts. After as little as a few weeks of such rearing, when the contact lenses were removed, the animals were blind. Cells in the eye reacted perfectly normally but the cells in the brain gave no responses to our stimuli, indicating that something had gone wrong with the connections between the eye and brain, or in the brain itself. In contrast to these remarkable effects in young animals , no adverse effects were seen when opalescent contact lenses were placed in adult cats and monkeys. This is exactly what we see clinically: adults humans who have had cataracts for many years see perfectly well when their defective lenses are surgically removed and replaced with glasses or implants.

We did similar animal studies aimed at understanding why cross- eyed children so often become blind in one eye. We simply cut an eye muscle at birth, causing the eye to turn in or out. The result was a major disruption of connections between the eye and the cortex. And again the deficits occurred only if the eyes were made crossed early in an animal's life. As a direct result of our work, ophthalmologists have learned that blindness in children can be prevented by operating to remove the defective lenses or straighten the eyes, as long as the operation is done soon after birth. Vision in the eyes of countless children has been saved by operating early. This is an important result, because cross eyedness is one of the most common causes of blindness in this country. It is also important in indicating that certain brain circuits can go wrong if they are not used early in life. It may not be too surprising if a child brought up in an orphanage, with little nurturing from adults, ends up unable to establish normal human relationships later in life.

It may be worth emphasizing that at the beginning we had no idea of setting out to prevent blindness. We tackled the brain because, as the most complex machine known, it seemed to us to provide one of the most challenging problems in all science. It was only after several years of studying the normal brain that we found ourselves in a position to ask what went wrong in cases of cataract or crossed eyes.

The potential fallout of work like ours of course goes far beyond learning how to prevent one kind of blindness. Research on the brain is producing, and will continue to produce, answers to abnormalities that include mental retardation, epilepsy, psychoses, Alzheimer's Disease, the effects of trauma, drug addiction and criminal behavior. Some of these problems may be solved by being addressed head-on, but most answers will continue to come from work motivated by curiosity and an urge to understand fundamental mechanisms step by step.

Since I began work in the 1950's, the field of neurobiology, like biology in general, has developed at a rate that no one would have dreamed possible 45 years ago. Some of this explosion of knowledge depended on advances in physics and chemistry that made it possible to record from single cells, and to unravel the mazes of nerve-fiber pathways in our brains. But much of the explanation for the progress has been sociological. Immediately after World War II, the leading country in brain research was probably England, with the U.S.A. not far behind. Today, more brain research comes from the United States than from all other countries in the world combined. This can be measured in many ways, but the list of Nobel prizes awarded to Americans year after year is probably as good an index as any. Why has the USA done do well? I can think of two main reasons. First, though much important research has been done in research institutes (such as the Intramural Program at the NIH), most of the medical research in this country has been done in universities, and our university system is by far the best in the world because of its variety, versatility and the freedom it gives young investigators to work independently. (We can thank our lucky stars that the university systems in Germany and Japan are such disasters!) Second, the period in which most of this spectacular progress has occurred is the very period in which biological research has been supported by the NIH. We can be grateful not only for the generous support, but for a system of peer review and research grants to individual investigators (the RO1's) that have made it possible for young people to dream up ideas and carry them out independently.

One can only hope that nothing happens to change all this. Unfortunately the past decade has seen some clear and ominous reversals. Today, about 80% of grant proposals are not funded, and meanwhile the time one spends writing the proposals has increased markedly, to the detriment of the work itself. I hope this represents a transient glitch rather than the beginning of a major trend. The sort of research I do is inexpensive compared to high energy physics or astronomy, but the yield in terms of new knowledge and preventions and cures of disease has been high. In dollars and cents fundamental medical research has paid for itself many times over. The problems still unsolved dwarf those already solved, but what is required is simply well-trained scientists, time, and a fair system that assures steady support to those who deserve it.

David H. Hubel, M.D.
John Franklin Enders University Professor of Neurobiology
Harvard Medical School

Dr. BISHOP. Now, Dr. Joseph Murray from Harvard.

There is no risk that I would misidentify his origin since he was one of my teachers when I was a student at Harvard Medical School.

OPENING STATEMENT—DR. JOSEPH MURRAY

Dr. MURRAY. Mr. Chairman, it is a real privilege and pleasure to be here with you and your committee. Organ transplantation, which is what I worked on for the first 20 years of my career, was once considered an absolute impossibility, going back to the times of the Greeks and the Romans. Now it is considered commonplace, and the young interns and residents coming through helping to transplant organs like livers, kidneys, hearts, lungs, just consider it another surgical operation.

How did this happen? Well, it was the combined result of work from many diverse bioscientific disciplines.

I happen to be a surgeon. As a kid growing up in middle Massachusetts in a small town, I just wanted to be a surgeon, go back to my hometown and take care of patients. During World War II, I was in medical school when the Japanese bombed Pearl Harbor. We were put into uniforms as privates, accelerated our course through medical school, were given a nine-month surgical internship and sent out to work for the military.

I was fortunate to go to Valley Forge General Hospital on a chance assignment. We took care of battle casualties from the African, European and Pacific theaters, and many of these casualties were severe burn patients, dying because their surfaces were uncovered and they were dying of infection and poor nutrition. In order to tide them over, these catastrophic burns, we took skin from unrelated persons to place it on them. They were often from cadavers, occasionally living relatives. We knew the skin graft from one person to another would not survive permanently, but they could survive sufficiently long to tide the patient over and save a life.

When I went back after the service—I was in for three-and-a-half years and got out of the service three years after VJ Day—I went back to Harvard Medical School, finished my training, and was very curious as to why skin from myself, if I took a piece of skin from one part of my hand and put it here, it would survive permanently. But if I took a piece of skin from Dr. Bishop and put it here, it would survive for a week, 10 days, maybe two weeks, but the body would recognize it as something foreign and reject it.

Well, I often wondered, how could the body be so smart? Because it could recognize my skin, distinguish it from anybody else's. So I got interested in a research project going on at the Brigham Hospital on the transplantation of kidneys.

Now, someone might say, how in the world did you all get started? Well, we got started because the chief of medicine wanted to study high blood pressure, and we have known for a century that high blood pressure was somehow associated with kidney disease. So the professor, Dr. Thorn, felt that if we could eliminate the kidneys, the diseased kidneys, we could cure high blood pressure. So the artificial kidney, so called renal dialysis, was first invented and demonstrated in the mid-1940s.

Well, this was only temporary. We all know that chronic dialysis is a way of treatment of end-stage renal disease now, but at that time it was unheard of. But we wanted something more permanent. So the more permanent way of substituting for renal function is to transplant kidneys.

So I worked in the laboratory. We were supported by grants from private industry and from NIH, and I developed a surgical operation in which we could transplant kidneys in dogs which would be perfectly normal. We had a whole group of dogs living on transplanted kidneys with perfectly normal function.

We then, in 1954 in the fall, happened to have sent to us at the hospital a pair of identical twins. One was dying of kidney disease and the other was perfectly normal and healthy. But we knew from experiments back in the mid-1930s by plastic surgeons in St. Louis that skin grafts between identical twins could survive permanently. They have the same genetic background. So therefore, it seemed reasonable to try to transplant a kidney between these identical twins.

Well, this was totally unprecedented. We were going to operate on a normal young man, take out one of his healthy kidneys, not for his benefit, but for somebody else's. This was a tremendous ethical and moral problem. We consulted clergy of all denominations, clinicians from other hospitals, we had the public in on the discussions. We finally decided it was reasonable to go ahead and take out a kidney from a normal young man and give it to his brother.

We used the same surgical technique that I developed in dogs. I had never done it in humans before, but this seemed reasonable to do. The operation was a spectacular success. The patient was alert by the next day. He was hungry for the first time, he had a spark to his eyes and he left the hospital two or three weeks later with normal renal function, and he functioned well for many years. This experience really triggered renewed interest around the world in transplantation.

So we, obviously, wanted to enlarge the prospects of transplantation, because after all, not many persons have identical twins that they can use as a donor. So we worked in the lab, me and my colleagues, with different aspects of the problem. I worked on mice, rats, rabbits and dogs, trying to extend renal transplantation beyond identical twins.

In 1959, this is five years after the first operation, the twin operation, we did get a successful transplant between brothers who were not identical twins. They were genetically different. We used total body X-ray therapy and bone marrow transplantation as a means of suppressing the immunity. That worked and that patient lived for some 25 or 30 years perfectly normally. But the method of achieving this was drastic, and we didn't have many other human successes.

At this time in the late 1950s, hematologists discovered that a certain anticancer drug was an immunosuppressive drug, in other words, it would suppress immunity. The drug was developed by Burroughs–Wellcome, Drs. Hitchings and Elion, as an anticancer drug. Well, the hematologist at Tufts University in Boston found it was an immunosuppressive. So we worked with dogs using this drug, and we were able in a large series of animals, some 800 operations that I did along with my group, to find out how we could use this drug effectively. We produced normal dogs running around the lab on one transplanted kidney and one of them even gave birth to a normal litter.

So we went and tried it on a human in April of 1962. Now, that is eight years after the original transplant, and this was successful. We took a kidney from a dead person, placed it in this human dying of kidney disease, and he survived. We published it in appropriate medical journals and this started transplantation worldwide.

Now, I don't want to intimate that we were the only group involved. After our first transplant, other groups elsewhere in the country and in the world took it up. And there are wonderfully productive groups in Denver, in New York City; Cooperstown, New York; Richmond, Virginia; Chicago; Los Angeles; Palo Alto; San Francisco; Minneapolis; Salt Lake; Jackson, Mississippi; Pittsburgh; Houston and New Orleans. All of these cities have active transplant groups by this time. And London and Paris and Edinborough had some original pioneers working on the problem. We were all a very closely-knit group trying to solve this problem.

Once we solved the problem with kidney transplants, others succeeded doing liver transplants, heart transplants, lung transplants, combinations of hearts and lungs, pancreas, the intestines have been transplanted successfully. Now, every major university in every city has a transplantation unit.

Now, all of this success in every organ was preceded by critical animal experimentation in the laboratory animals before use in humans.

Now, currently throughout the world there are hundreds of thousands of patients with transplanted organs leading productive lives; 300,000 kidney transplants alone.

May I say that I only have one exhibit because I think one person is better than thousands of statistics. You see in the middle two young women, Edith and Wanda, Edith Helm and Wanda Foster. They live in a small town outside of Oklahoma City, I think the name of it is Davenport. And Edith is the world's longest living kidney transplant patient. I operated on her in May of 1956, taking a kidney from her sister, who is to our left.

At that time, they were both married only three months. Their husbands were in the service, I think the Korean War, they were Korean War veterans. We did the transplant, and there was a particularly difficult medical moral decision, and I won't go into details, because there was a minor defect in the health of the donor. But anyway, both are alive and well today. She is the world's longest living transplant of any organ.

She had a pregnancy, unexpected. We were worried to death, we thought maybe it might affect the transplanted kidney. But fortunately, she gave birth, we actually put her in the hospital and did an elective caesarean to be certain, but we found out later that we could have had a normal vaginal delivery. Anyway, she has had children and grandchildren and I visit them frequently when I go to Dallas to see my son and daughter-in-law, and one of those grandchildren is teaching high school in Davenport, Oklahoma.

Now, these transplants not only have been examples of spare-parts surgery, they have led to many other unexpected dividends.

They have led to tissue-typing, using white cells, they have led to earlier diagnosis of congenital metabolic diseases, such as the disease that Dr. Brown has mentioned; and the spinoffs from transplantation far and beyond spare-part surgery have been tremendous.

Now, all of these advances have been produced by clinicians. I am a surgeon, I made my living as a surgeon, I love to operate, I am very fortunate to have been gifted and have all of the wonderful educational background that I have had. And I love taking care of patients. That is my primary mode of living. But I have worked with scientists, collaborative throughout, worked with geneticists, immunologists, microbiologists, pathologists, physiologists and it has been a marvelous life as far as I am concerned.

Now, people often ask, what is the next major advance in transplantation? I haven't the slightest idea. People ask, did I think 40 years ago that transplantation would be as far as it is? The answer, of course, is no. All we were trying to do is save the life of a patient, or the lives of patients. But I do know one thing. None of this would have occurred without the solid support for not only basic science, but for clinical scientists working collaboratively.

Thank you.

Dr. BISHOP. Thank you.

[The prepared statement of Dr. Joseph Murray follows:]

Statement to the House Appropriations Subcommittee on Labor Health & Human Services
Rep. John E. Porter, Chairman
February 28, 1995
By Joseph E. Murray, M.D.

Mr. Chairman and Members of the Subcommittee:

Today organ transplantation is commonplace. Not long ago, it was considered impossible. The past four decades have fulfilled dreams of "spare-parts surgery", dreams going back to the Greeks and Romans. This major bio-medical advance in transplantation biology over the past forty years is the combined result of work from diverse bio-scientific disciplines. There is a basic unity in scientific research which transcends arbitrary boundaries between disciplines classified as "basic", "applied", "targeted," "clinical", "bench", or "bedside." Over a century ago Pasteur described this sense of unity:

> "No category of science exists to which one could give the name of applied science. Science and the application of science are linked together as a fruit is to the tree that has borne it."

The story of transplantation is a striking example of diverse scientific disciplines participating in a common enterprise that has produced benefits to a mankind far greater than any single discipline alone could have done. It all started when clinicians tried to find better ways to treat patients with renal failure.

First hemodialysis, the so-called "artificial kidney" was developed, but this was at best only a temporary help. We clinicians needed something better, a treatment that could be permanent. After several years in the surgical research laboratory of Harvard Medical School, I was able to produce in dogs a predictable surgical model for permanent renal transplantation.

In 1954 monozygotic (identical) twins, one healthy, the other dying of kidney failure, were referred to our hospital for possible transplantation. After thorough discussion with the twins, their family, other physicians, clergy of all faiths, and hospital and medical school trustees, our team acceded to the patients' and family's request that we proceed with the surgery.

In December 1954, we removed a normal kidney from the healthy twin and transplanted it into his dying brother. The result was an immediate complete success. It encouraged us, and others around the world, to continue this avenue of research. I spent the next five years performing experiments in mice, rats, rabbits, as well as dogs, trying to extend renal transplantation beyond identical twins.

In 1959, we did achieve a successful transplant between genetically diverse brothers. At that time we were using total body x-ray treatment for suppression of immunity. This was the world's first successful organ allograft, the identical twin having been an isograft, i.e. a transplant between genetically identical members of the same species. During these years we continued to work closely with immunologists and physiologists.

Our ultimate goal was achieved in 1962 when we transplanted successfully a kidney from a cadaver to an unrelated patient. To suppress the recipient's immune response, we used anti-metabolic drugs, originally synthesized by Drs. Hitchings and Elion of Burroughs-Wellcome,[1] as anti-cancer drugs.

During these years we collaborated closely with biochemists and hematologists. Our lab group and I performed over 400 renal transplants operations in dogs to be sure of their safety before using them in humans.

At this time, many others groups in the USA and elsewhere were also working on transplantation. These include groups in Denver, New York City, Cooperstown, Richmond, Chicago, Los Angeles, San Francisco, Palo Alto, Minneapolis, Salt Lake City, Jackson, Pittsburgh, Houston and New Orleans, as well as London, Paris and Edinborough.

Successful transplantation of liver, heart, lung, heart-lung, pancreas, intestine, and bone marrow followed in the next two decades. Success for each organ was preceded by critical animal experimentation in laboratory animals before use in humans.

Currently throughout the world, hundreds of thousands of patients with transplanted organs are leading productive lives. In addition to saving lives, transplantation biology has produced unexpected beneficial spinoffs. For example, heart transplants can serve as prototypes for some types of heart disease and lead to earlier diagnosis and prevention. Better diagnosis and treatment of congenital metabolic diseases are now available.

All of these advances have been produced by clinicians and bench scientists from many discipline working collaboratively. I cannot predict where the next major advance in transplantation will come from. But I am certain that human transplantation would never have occurred without the sharing of knowledge between clinicians and non-clinical scientists.

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[1] Hitchings and Elion received The Nobel Prize in 1988 for their syntheses of a wide variety of drugs, i.e. anti-malarial, anti-cancer, anti-viral, anti-metabolic, as well as immunosuppressives.

Dr. BISHOP. And now Dr. Phillip Sharp from MIT. Phillip.

OPENING STATEMENT—DR. PHILLIP SHARP

Dr. SHARP. Mr. Chairman, Members of the subcommittee, it is a pleasure to have this opportunity to appear before you and discuss the Nation's science. My interest in participating in this event made me break a rule of 20 years at MIT. I have been a professor there over this period of time and this is the first time I have canceled a lecture in 20 years. Don't worry, the brightest and the best are not going to suffer in terms of their educational advancement. They have assigned readings, and I will be back on Thursday.

Approximately 18 years ago, in 1977, my colleagues and I, supported by a grant from the National Institutes of Health at MIT, had the good fortune of making a discovery about the structure of human genes, and the discovery was that the structure of our genes are fundamentally different than the structure of genes that had previously been analyzed in bacterial systems. Richard Roberts at Cold Spring Harbor led a group who came to similar discoveries at the same time.

I want to illustrate that, because it is a fairly fundamental discovery. And I will do it using a piece of rope here. This rope represents DNA. Jim Watson, who is sitting beside me here, may not recognize it. The models he has at Cold Spring Harbor are much more elegant than this. But what is interesting about the structure of our genes is that the sequences that are part of the genes, that code for protein and therefore make them important, and therefore the reason mutations have effects, are represented here by blue tape. And you will note that in this model, the blue tape for this single gene is interrupted by yellow sequences, meaning that the sequences, which necessarily have to be put together to make a functional gene or sequence from a gene, have nonsense sequences as part of a mosaic or split gene structure.

Now, how these sequences are assembled is a process called RNA splicing where the DNA is copied into an RNA intermediate, and then that RNA intermediate, which I will illustrate here with the rope, is spliced, in that the nonsense yellow sequences are removed and the sense blue sequences are spliced together. So this splicing process occurs in the expression of almost all of our genes. In fact, your typical gene has 8 to 10 of these nonsense sequences in it, and no more than maybe 5 percent or 2 percent of your total genetic information is likely to be sense, and the rest of it is likely to be these intervening or nonsense type structures.

Now, you may ask why we have such a gene structure and I could spend an hour or two telling you about speculation that is set in the context of evolution, but I won't do that. I will make a point out of this insight, and that is the date of the discovery of split genes was in 1977, and that means that only 20 years ago, a little less than 20 years ago, we gained an understanding of how our genes are structured, and therefore, we could begin to think of how our genes have a role in processes such as cancer, as Mike Bishop has described, or in heart disease as Mike Brown has discussed. Therefore, it has only been over these last intervening 20 years that we have had sort of the modern cell biology of human disease, and we have made progress in understanding the nature of the genetic underpinning of diseases and how we might treat cancer and heart disease and other things.

But it has only been 20 years, and the amount of ignorance in this field is still very vast. There are many things to be discovered, and our ability to translate this information into new treatments and new preventions is something that is really quite primitive at the moment. So with this new knowledge will come opportunities to improve public health, as well as increase our economic competitiveness.

I want to illustrate another implication of the structure, the split gene structures of genes and the RNA splicing process. I will use as an example a genetic switch that is important in the reproduction of the AIDS virus, HIV.

We have been studying this process in my laboratory because we have been studying the RNA splicing process over the last 15 years. And during expression of the AIDS virus, its genetic information also can be illustrated as this piece of rope. And the virus, once it infects a cell, its information is also spliced and big pieces of the viral genome are removed, and a multiply spliced part of the RNA is expressed in the cytoplasm of the cell.

From this form, a protein called Rev, a viral protein, is expressed that then goes back and expresses the splicing process, then producing inefficiencies in RNA which is part of the new virus particle that spreads in the body and creates the immune disease of the deficiency in immune function.

So we have been studying this process by which viral protein controls, Rev controls the replication of the virus. I am sorry that we don't understand it completely. We study it with the hope that this new information will lead to new ways of controlling the spread of the virus and new possible drugs and treatment of the virus.

Now I wish I could stand before you and state that I and my colleagues have mastered this disease. However, we can't cure AIDS and we may not be able to for many years. The search for a better understanding of the disease and for better treatment continues.

However, I want to emphasize that the discovery of AIDS as a virus and the subsequent tests of that, which came out of biomedical science, has enabled us to eliminate it from the donor blood system, by and large, and it has increased the awareness of how this virus is spread in terms of blood-borne transmission. And therefore, we have had an impact on the disease even without being able to have a cure of it.

Nevertheless, the spread of this virus is still occurring in our society. It is increasing at approximately 3 percent per year. There are 1 million people infected in this country, tens of millions of people infected across the world with this virus. It is a new and emerging virus in human populations and, therefore, we don't fully understand how this virus will evolve in time, given its spread in the human population. So further study of this virus will be critical for the public health of this country.

In the last few moments of my talk, I want to mention another practical result of the discovery of split genes and that is its relationship to biotechnology. Since the structure of genes in bacteria and human cells is fundamentally different, the production of human proteins, such as growth hormone in bacteria, requires the conversion of this split gene structure to the nonsplit gene structure of bacterial systems. This type of knowledge and the revolution of recombinant DNA resulted in the emergence of the biotechnology industry in the late 1970s.

A group of small companies was formed by the interaction of businessmen, venture capital and Wall Street financing with university-based technology, by and large, supported again by the National Institutes of Health across the country. The main focus of this interaction was to translate this new knowledge, biotechnology, into useful products that could be used by society.

We are still in the early stages of biotechnology. Its first series of products emerged in the market in about the last 5 to 10 years. These include growth hormone produced in bacteria, insulin to treat diabetics, erythropoietin, interferons, cytokines, such as colony stimulating factors to support cancer patients, tissue plasmogen activators to treat heart disease, vaccines for hepatitis B to eliminate this spreading viral infection, diagnostic tests for hepatitis C, probably a vaccine for C in some time.

The products from biotechnology now command over $10 billion worth of sales, and this is growing steadily. The industry employs about 100,000 people across the country. And in addition to these small companies, large companies across the country and across the world are incorporating biotechnology into their technology base and producing new and interesting products. It is not difficult to imagine that as the country moves to a time in which there are increasing energy costs, the use of biotechnology and processes that are renewable to produce fine chemicals, pharmaceuticals, and other materials will become increasingly important.

I want to end by thanking you and the committee for this opportunity to discuss my science. There are numerous other scientists across the country who could equally well make a valid case for the impact of their science in terms of its usefulness in the country. I hope that as its representatives you will be able to continue to nurture and support and encourage a vigorous scientific and educational community. Information and knowledge are the gold of the future, probably the only gold this country has, and this country must remain a pioneer in seeking these riches.

Thank you.

[The prepared statement of Dr. Phillip Sharp follows:]

APPROPRIATIONS SUBCOMMITTEE HEARING

Phillip A. Sharp
Salvador E. Luria Professor
and Head of the Department of Biology
Center for Cancer Research
Massachusetts Institute of Technology

Mr. Chairman and members of the subcommittee,

It is a pleasure to have this opportunity to appear before you and discuss our nation's science. My interest in participating in this event made me break a rule that I had maintained for the 20 years I have been a professor at MIT - this is the first time I had to cancel a scheduled lecture for a course. Please do not worry that the education of the brightest and best is being compromised however. The students have assigned readings.

Approximately 18 years ago during the spring of 1977, my colleagues and I had the good fortune of discovering that the structure of genes in human cells was fundamentally different from the structure of genes in the simpler organisms like bacteria. A group at Cold Spring Harbor led by Dr. Richard Roberts came to a similar insight at the same time. We, independently discovered that genes in vertebrate cells were split where sense sequences were interrupted by nonsense sequences. I will illustrate this with two pieces of yellow rope. The rope represents the linear strands of DNA, the genetic material. The blue tape represents the sequences in the gene which code for a protein such as the keratin in our skin. In bacterial genes, all the sequences for a specific protein are contiguous. However, in our genes, these sense, or "blue", sequences are interrupted by nonsense, or "yellow", sequences. The gene is split or mosaic in structure. A typical gene in our cells has 8-10 nonsense interruptions, or introns. The sense segments are called exons.

The date of the discovery of split genes, 1977, is quite important in that before it, we did not know the structure of human genes and how they might function in cancer or heart disease. Thus, in a true sense, modern cell biology or the science of human cells is less than 20 years old. We have learned a lot in these 20 years but our ignorance is vast and our ability to convert the emerging understanding into effective treatments is primitive at best. When you read your morning newspaper about the newest amazing discovery concerning biology or medicine, you should remember the many unknowns that lie before us. Every new discovery opens up a new territory to be explored and each discovery in turn results in the acquisition of knowledge that can be used to improve public health care as well as increase our economic competitiveness.

Let me illustrate for a moment some of the implications of the discovery of split genes and the RNA splicing process which removes the nonsense introns and joins the sense exons. I will use as an example the genetic switch which controls the reproduction of the HIV or AIDS virus. We are studying this switching process in my laboratory in the hope that it will provide insights into how to develop drugs or other means to inhibit the replication of the virus after infection. When the HIV virus infects cells, its genetic information is expressed as RNA which is multiply spliced. I can illustrate this again using the rope where the first exon is spliced to the third producing one type of RNA which specifies the production of a protein called Rev. This protein triggers a switch in the RNA splicing process. By a mechanism we still do not fundamentally understand, the Rev protein inhibits the splicing process so that intact viral RNA is produced and virus can be formed and spread to another cell. This continuous amplification of the virus is thought to be responsible for the destruction of the immune system and for the terminal AIDS syndrome.

I wish I could stand before you and state that my own research or that of my colleagues has mastered this disease. However, we still cannot cure AIDS patients and may not be able to for quite a few years. The search continues for a better understanding of the disease and for better treatments. The discovery of the AIDS virus and subsequent tests enabled us to eliminate it from donor blood and to increase awareness of the nature of blood born transmission of the virus and thus reduce the frequency of its proliferation. Nevertheless, even here there is much more to do as the number of people infected is increasing at a rate of 3% each year.

In the last few moments of my talk, I want to mention another practical result of the discovery of split genes and that is its relationship to biotechnology. Since the structure of genes in bacteria and human cells is different, the production of human proteins, such as growth hormone in bacteria, requires conversion of the split gene for this protein into a contiguous gene. This type of knowledge and the revolution of recombinant DNA technology resulted in the emergence of the biotechnology industry in the late 70s. A group of small companies was formed by the interaction of businessmen, venture capital and Wall Street financing, with university based technology. The main focus of this interaction was to translate the new knowledge coming out of universities into products that will improve both health and the economy of the country. Although we are still in the early stages of biotechnology, its first series of products have entered the market place, i.e. growth hormone, insulin, erythropoietin, interferons, cytokines, such as G-

CSF, plasmogen activators, vaccines for hepatitis B and diagnostic tests for hepatitis C. The products from biotechnology now command 10 billion dollars of sales each year and this is growing steadily. The industry employs about 200,000 people across the country. In addition, many larger companies have begun to develop biotechnology as part of their technology program. This will lead to new ways of producing an ever expanding assortment of fine chemicals and agricultural products in the future. It is easy to picture a future where, with increasing costs of energy sources, the nation will need to turn to renewal based processes to generate materials for industries such as construction and clothing and for personal care. In this setting, biotechnology will become an increasingly important part of society.

I want to end by thanking you and the committee for this opportunity to talk about my science and how it relates to our national needs. There are numerous other scientists in this county who could make an equally valid case - I am simply one of many, and proud to be their colleague. I hope the country through its representatives continues to nurture, support, and encourage a vigorous scientific and educational community. Information and knowledge are the gold of the future and this country must remain a pioneer in seeking their riches.

Dr. BISHOP. Dr. James Watson from Cold Spring Harbor Laboratory on Long Island.

OPENING STATEMENT—DR. JAMES WATSON

Dr. WATSON. Mr. Chairman and Members of the subcommittee, I am going to depart from my prepared speech. Harold Varmus read it and said it was pretty dull. So I thought I should—he said to get a little more personal. And so I will go through several phases of my life in trying to point out where NIH was important and not important.

The first was that when I was in college, I was very interested in living organisms, particularly birds, and I really wanted to know what the essence of life was. And I was sort of at a loss until I read a book by a physicist which said the essence of life was the gene, which provided the information that gave us our defined characteristics. It was our genes, which you know, made us humans and not monkeys, and so I really was curious what the gene was. So I went to graduate school, and at that time I learned that the gene might be associated with a molecule which they called DNA. They didn't know what DNA was, so I wanted to find out what DNA was and that took me to Europe. It took me to Europe, and particularly to Great Britain, because that is really where they were most advanced, and had the techniques where you might find the structure of DNA. Very luckily, in came a very tall Englishman, Francis Crick. We discovered the double structure of DNA.

I then came back home and after a few years became a professor at Harvard, and it was wonderful. I had good students, and it was very easy to get money. Just apply for grants, you didn't have any anxiety whatsoever about money. You had anxiety, of course, as to whether we were going to be clever enough to make the next step forward and find out the rules by which genes worked. And that went very fast, and within a period of less than 20 years we had worked out the rules, and you could sort of summarize these rules by saying we had the genetic code.

And by the time this had been worked out, the leader in this research was the United States, and it was really because NIH let us expand, let us have these opportunities of following up DNA, and we are extremely grateful to Congress for really taking the lead. It wasn't the Administration; it was Congress who said NIH is a real defense for our country, we have to find out about living things. So we had an absolutely golden era.

This golden era led quite unexpectedly to scientific things, which led to an even greater golden era, that recombinant DNA in 1973 was a result of a lot of work. Suddenly, we had these tools to look at genes. We couldn't do it before. We could find the general rules, but we couldn't take the human gene, and if you said, "Well, how far are you getting toward understanding humans," we weren't very far. But suddenly we had the tools.

And these tools have been applied to a number of diseases, and you have heard them from Mike Bishop, and here again I should say that not only did Congress sort of really let NIH get going, but in 1972, I think it was 1972, the War on Cancer started. Congress decided we really should find out about cancer. And I came down here and testified at that time about what we could do, and suddenly we were given, at least for a couple of years, more money than we knew what to do with—to work on cancer.

Well, when there is more money, people run toward it. Suddenly cancer research, which really had not been very heavily populated, the best medical researchers in the United States—I can't say all of them, because Mike Brown did something else—but an awful lot of them took on the cancer problem. My laboratory at Cold Spring Harbor took it on, and now 20 years later Mike Bishop made a statement which takes courage, but yet he is no fool and he is not dishonest, that he thinks we are going to cure cancer.

Now, this is a result of an enormous amount of good science, and what we have learned is that cancer is very complicated. I mean, even though he talked about accelerators and brakes, there are an awful lot of brakes and an awful lot of accelerators and the interactions are pretty subtle.

As a result now, we don't have enough money for cancer research because there are so many things that we want to do, so we are in a bind. I run an institution and you know, I just think about money. I wish I was thinking more about science. But my job is, you know, to keep my younger scientists from always thinking about money. So I have to raise the money.

And so that is where we are in cancer research. But it was really because of Congress saying, you know, we are optimistic, put America's best toward a difficult problem. Of course, we didn't know how difficult it was, and that is true of many things. But we have succeeded.

Now, another thing which the human recombinant DNA revolution gave us was the possibility of eventually working out the complete genetic instructions of a human being. When they first learned how to sequence DNA about 1976, we thought, well, some day it will be done. But I think none of us expected that within 10 years after that discovery there would be serious discussions of whether the time had come to go for it. At first I was like a typical scientist—oh, the time hasn't come. But I listened to my friend Rinaldo Dobecco and he came to us and he said we should do the project. I had worked with Rinaldo 20 years before and he was right. So within a couple of months I had ceased being a skeptic and I thought, gee, we have to do it because when you really look at it, besides cancer, which is due to changes in genes largely which occur after we are born, there are so many diseases which have genetic components—diabetes, Alzheimer's, asthma, arthritis, atherosclerosis—to really understand why some of us come down with one disease and not another, we are going to really have to look at our genes.

And we said, well, great objective, but it costs too much money. But you came to our rescue again. You essentially voted money to start the Human Genome Project at a time when the scientific community really didn't appear in front of you. Few of us did; by the time I appeared, I was getting old. And by getting old, I began to think do I want to be sick when I am in my seventies? You know, I was getting close. So you know, I began to think about Alzheimer's and these various things and thought the only way you are really going to find out about them is to get the genes.

Now, the Human Genome Project has been going on now for less than seven years, and besides voting the money, I was very privileged to be asked to help lead the NIH component of it, and in that capacity I appeared in front of this subcommittee several times. And now it is a great pleasure to be in this room with Francis Collins who succeeded me and is I think an equally firm component of the grandeur of this objective, of really understanding our genes so that we can understand our diseases.

And the discoveries are just coming at an unbelievable level. One week leads to one thing and now someone at Rockefeller University has found a gene that they think makes some of us fat. And a lot of people care about that. I can give you an instance. It is a rumor, but it is reputed they want to sell the gene for close to $50 million. This just indicates there is money in these things, because we are coming really close to finding out very important things which can make our lives more pleasant by making us thin. Being able to eat and still be thin, I mean a wonderful objective. Now I just know I have to not eat to sort of try and look like I did when we found the DNA structure.

But it is a big project. And Francis Collins made me take out a word. I said it was a mega project. Well, yeah, why not be grand, so I took out mega project. You will find it is not in my testimony. People are frightened by, saying things are big.

But the human body is very complex. And particularly when we get to our brain, it is unbelievably complex. But the happy news is that through, again, NIH, enough people have been trained that we really can go after this complexity. We don't know enough about Alzheimer's to say that we are going to stop it, but at least there are rational ways. Drug companies are spending their money in rational ways because a protein called a apoE protein E has been implicated by work at Duke University to be strongly involved in this disease, and why not stop it.

And so I think we shouldn't be afraid to come in front of you and say that the result of our work is we sort of know the face of the enemy and he is a little bigger than we ever guessed. And so we are going to do what I think the American people want us to do, to spend an amount of money proportional to realize our problem and to spend it well.

I think this is the one thing I want to say. We spend it well. I think if you look at other ways in which the Federal Government spends its money, you can always find someone who is taking a secretary along to a meeting or something. You always find one or two bad instances, but they are rare. And you know, we really aren't wasting money. And if we had more money, we wouldn't waste it either. And I think it is your decision, as representing the people, how much faith you want to place not on us, but the younger people that we train.

In sort of looking around, I think what medical science has done is it has made it possible for people to live in their seventies and actually be happy. If your hip is gone, you can now replace it. If your kidney is gone, you can replace it. You know, there are heart valve operations. So the seventies are okay. I mean, if you are lucky. But your eighties are going to be dreary. So I think if you want to say what the objective of Congress should be, it is to make the eighties tolerable some 20 years from now. Not for me, I guess it is going to come too soon. But I think there is the opportunity to really think big, think grand, and succeed.

Thank you very much for having me.

[The prepared statement of Dr. James Watson follows:]

Testimony of James D. Watson, President of the Cold Spring Harbor Laboratory, before the Labor, Health and Human Services Subcommittee of the House Appropriations Committee
February 28, 1995

I am honored again to give testimony before your illustrious committee now chaired by Congressman John Porter. Historically your actions and those of your sister body in the Senate have played vital leadership roles, sensing opportunities for important medical advances before they were widely appreciated elsewhere, either by past administrations or within the biomedical research community. It was Congress, for example, that decided that the time had come in 1972 to declare War against Cancer and in 1988 to initiate the Human Genome Project. At these respective times, there was far from unanimity within the scientific community that the moment had yet arrived for such ambitious objectives. Neither project would have gotten going had not the members of these Committees been visionaries in their belief that advancing the health of the American people would come only through advancing biomedical research.

We can only shudder if we think where we would now be in our efforts to cure cancer if the war against it had not been declared more than twenty years ago. Within this interval we have produced a solid intellectual framework as to the nature of our pernicious foe, the cancer cell, and at last almost know the many, many faces of the enemy that we must hold back and then destroy. As a result, cancer researchers can at last think rationally about the molecular targets for the drugs we need and begin to work with our pharmaceutical colleagues to see that they are developed. Even with all this progress, however, the tasks that lie ahead pose deep uncertainties, and we must maintain the grandeur of vision that lets us start this battle which history will reveal as one of the major turning points of human history.

The goals of the Human Genome Project are equally daunting -- to identify all the human genes so that we can begin to understand how imperfections in their genes lead some individuals to be predisposed to major diseases like diabetes, asthma, or Alzheimer's. While it has long been believed that the various cancers arise because of genetic changes in normal cells, we have only recently begun to obtain firm evidence that genes also play major roles in the etiology of most human diseases that are not due to infections by viruses and bacteria.

That we can now show real genetic origins for so much of human disease is a consequence of the recombinant DNA revolution that commenced in 1973. Before it occurred, we had no way to map specific disease genes to specific sites on chromosomes nor afterward to isolate these genes and determine their structures. Happily strong clues about gene functions often are quickly seen by mere inspection of their respective structures. But even with the immense power of recombinant DNA methodologies, the eventual isolation of most disease genes still seemed in the mid 1980s beyond human capability. Only if we replaced the then virtual cottage industry approach to gene finding by a well-organized mega project, that hopefully would be broadly international in scope, would we be able to find most of the disease genes that play havoc with so many people's lives.

Serious discussions as how a Human Genome Project should be organized began in 1986, with specific reports as to its feasibility commissioned by the National Academy of Sciences, the Department of Energy, and the Office of Technology Assessment of the U.S. Congress. From the start the project had broad appeal, being seen not only as a means for speeding up medical research but also for insuring that the United States remained in the forefront of DNA technology development. Late in 1987, Congress voted monies to start up the Human Genome Program with both the Department of Energy and the National

Institutes of Health, and by the following fall expanded genome monies were distributed. Over the next two years, both programs were ramped up rapidly, allowing the Human Genome Project to officially start in October 1990, with its goal being to finish the complete sequence of the human genome by 2005. Then, and still now, the projected total costs were not to exceed three billion dollars, that is, one dollar for every base pair in the 3 X 109 base pair human genome.

Partly because it was so clearly a super project, where the desires of the individual scientist would partially have to be encompassed within a much broader collective vision, the Human Genome Project was initially opposed by the majority of molecular biologists, the very scientists who possessed the intellectual skills for its successful fruition. In their eyes, the Human Genome Project would divert scarce monies from the discovery of new basic principles which they have always seen as their main mission. In retrospect, their views were very short-sighted as it soon become apparent that the discovery of disease causing genes often leads to totally new ways of thinking about normal as well as diseased cells.

For example, the isolation of the gene that causes some individuals to be highly at risk to Lou Gehrig's Disease revealed the totally unexpected fact that a change in the structure of the enzyme superoxide dismutase by itself starts the progressive changes which characterize the dreadful neurological disease. While we have a long way to go before we will know the way this altered enzyme works, we have at last the first solid clue as to how this disease gets started. Equally unexpected was the discovery of the genetic cause of the fragile X syndrome, the most common form of inherited mental retardation in children. This proved to be a previously unknown type of mutation, a region of DNA that is unstable, grows in size and disrupts the proper working of the gene. That this mutation can now be detected has important implications for the families of these children and potentially for educational and social policies. There is some evidence that other human behaviors such as anger have a genetic basis, and through the window that the gene provides, we may see the workings of the neural circuitry and neurotransmitters that are immediately responsible for such behaviors.

With the pace of the Human Genome Project ever-increasing, virtually every week brings forth the discovery of one or more new human disease genes and as they later become cloned, we will often have completely new ways to think about the development and functioning of the human body. For example, there is now good evidence that the reading disorder, dyslexia, is sometimes due to an abnormal gene located on chromosome 16. Clearly we want to isolate it as soon as possible.

The best way to insure that this gene, and the many others that human society badly needs, are isolated as soon as possible is to promote the completion of the Human Genome Project within its 15 year time goal if not sooner. Happily this effort is no longer controversial in the world of molecular biology, and virtually all its former scientific opponents, who have the talents to help it go even faster, are now on its side. The moral here is that most scientists, though often viewed as irresponsible radicals, are in fact conservatives in nature and not prone to commit themselves to projects which demand big leaps into the unknown.

We have no choice, however, as human beings but to take on the challenge of understanding ourselves better as normal, well-functioning individuals as well as the victims of genetic disease that bring pain and sadness to all connected. No longer, however, should we see ourselves as tiny pawns in a play which we did not write. Instead the American people should now use tools of biomedical research to let us go into the 21st century with the expectation that our children and those they give birth to will have even healthier lives than those of us who have had the good fortune to be the Americans of the twentieth century. With the world always changing, only trying to stay the same means going backward.

Happily the Human Genome Project, through its identification of all the approximately 100,000 human genes, will create countless new opportunities for even more profound analyses of the human body and its diseases. We will face over the next decade a steadily rising number of new research leads that our biomedical research community will want to follow up, believing that they might have the chance to finally come to grips say with the essence of why different humans age at such different rates or with the nature of the neurotransmitter changes that cause victims of bipolar disease to erupt into uncontrollable mania. Real decisions have thus to be faced as to how to find the monies needed to make such great leaps forward. Clearly we have to re-examine our current funding portfolio to see what lines of research may have played themselves out and are not likely to lead to major leaps forward. If we don't rise to this challenge in these times of fiscal austerity, we will be failing those on whom our real futures rest.

On the other hand, we must realize from the start that even drastically cutting the less bright parts of our scientific portfolio will not release sufficient funds to let us truly come to grips with the extraordinarily complex and equally wonderful complexity of human beings. In particular, the working out of how we use our brains to perceive, memorize, and learn is the ultimate challenge of biomedical research for the 21st century. But here we must realize that the inherent complexities of the human brain are likely to be now grossly underestimated. Toward this end the Human Genome Program will provide an enormous resource toward helping pinpoint the many, many key genes involved in brain development and functioning.

To conclude, these are times when we must be led by our visions of what the future should be and not shirk our responsibilities to our children and to the generations that come after. We must always remain receptive to the most far-reaching of our dreams, using both our brains as well as our hearts to see that the ideals which have made us so proud to be Americans continue to dominate our actions. The biomedical research community looks now, as in the past, to this Committee for its continuing leadership in realizing those ideals.

Mr. PORTER. Well, let me begin by thanking each one of you for taking your very valuable time and spending it with us this morning and this afternoon. And I have to say, I have never seen so many Members of Congress quiet and attentive for such a long time. I only wish that our schedules were such that all of our Members could be here to hear you this morning.

I have to say to Dr. Sharp, we do appreciate that you canceled a lecture for the first time ever. Having once been a student at MIT, I can assure you that your students are happier, at least briefly. But they will make it up.

I thought when we first began this morning that we might be able to not talk budget, but this is the Appropriations subcommittee that funds NIH; there is no way we can avoid talking budget. Each of you have pointed out in different ways how important it is that we make the investment in biomedical research and that we continue our commitment. And Mr. Obey in his comments raised the issue very strongly, as it was right to do, I believe.

I want to take a moment, if I may, to respond to what he said, and that is that I believe in the end we will not cut taxes. I think that we are wise enough to realize that that is not affordable, even though it is politically popular. But that we will, in fact, work and bring down our deficits and balance our budget. There is nothing that I can think of that is wrong with having the present generation of Americans pay for what they receive, whether it is biomedical research or welfare or anything else, rather than forcing future generations who don't get the benefit to pay the bills for them. And I think all of us in America have finally realized that. It will be a tough budgetary time in a certain sense for every priority, no matter how high, to address this national problem and put ourselves back on a sound economic foundation for future economic growth and a better life for everyone.

I was struck by the fact that as we talked, we are committing more money to biomedical research than ever in our history through NIH. We were talking as if our commitment is gone. It is not gone. It has grown. It has grown continuously. It has grown in a bipartisan way through both parties. The national understanding of the importance of biomedical research is strong, although I wish it was considerably stronger. I would say that looking at the level of support and hearing of, as we know, the fact that only 20 percent or so of grants are actually funded, that is those that are thought to be meritorious are funded, we know that part of the reason is that the average grant is longer in time than it used to be. The other part of the reason is obviously that there are more meritorious grants to be funded.

SCIENTIFIC POSSIBILITIES AND FUNDING SOURCES

And we know that. I think we know that in terms of delivering medical technology to the American people the advances in technology have outstripped our resources, our ability to provide them to everyone, and now I think we are seeing the same kind of thing with respect to biomedical research. We have moved so fast in such a relatively short time and the possibilities are so great, we may be facing the prospect of not having the resources to fund all that is exciting and available and possible to fund. I wonder if you would address that question itself and tell us what your thoughts are about the potential and where we get the resources to fund all that may be there.

Dr. Bishop, do you want to start and comment on that?

Dr. BISHOP. I would like to make first a point about what it costs to bring improved technology, and I want to do it with a personal reminiscence.

When I was young growing up in rural Pennsylvania, the most dreaded disease was something called poliomyelitis, infantile paralysis. My parents kept me house bound for two months every fall, the dog days. I couldn't go to the swimming pool. I couldn't play with other children. We were terrified that I would get this paralyzing and sometimes lethal disease.

Within the decade of my adolescence, it was possible to keep people with poliomyelitis alive by putting them in iron lungs, in intensive care units at the time for a month, two months, three months, until the disease had run its course. This was an appallingly expensive process, which if projected at current dollars, would be staggering. And observers at the time I am sure said, you see, improve medical technology, and the costs go up.

And then John Enders came along with his colleagues and found a way to grow that virus in a simple way in a laboratory. He and others found a way to make a vaccine, and iron lungs disappeared from our hospitals, disappeared from our technology.

The year I became an assistant professor at the University of California, San Francisco, testimony was given to this subcommittee—I couldn't possibly tell you who chaired it—which gave an accounting of what it had cost to develop the vaccine, what it had cost to deploy it, and what it was now costing to deploy it, and what was being saved by way of not only medical costs, say, in intensive care units, but lost years and wages. I have that file somewhere. And some years ago for my medical students, to dramatize for them the importance of research—it is sometimes difficult to convince medical students that research is important—I projected the numbers from that testimony to the contemporary economy, using numbers I got from the New York Times. I calculated that the polio virus vaccine now saves us about $30 billion a year in medical costs, lost wages, et cetera, and you can well imagine that it costs only a tiny fraction to use it.

So the point is that you look at an intermediate technology and you may see big costs as in cardiovascular disease, big costs, all those removals of obstructions, heart transplants. But if you look to the decisive solution that Mike Brown talked about this morning, you see huge savings.

And we have to move beyond intermediate technology. We have to have the faith that we can move from the intermediate technology to decisive solution in each disease; we can see that in cardiovascular disease. We can see it coming in cancer. I think only then is the accounting fair. That is my point. Only then is the accounting fair.

Now, where is the money going to come to make that move? I am a taxpayer, and I for one am willing to provide it. I am willing to pay more taxes. My wife is willing to pay more taxes. We talk about this all the time. I want Congress to use those taxes wisely, but although I am not an economist, for the last few years I have seen our government do some remarkable economic things.

We found more than $500 billion overnight to bail out a dubious fiscal industry. We just found $50 billion to help Mexico almost overnight. We found the money to fight a totally unanticipated war in the Persian Gulf, and all of these are efforts on a magnitude far exceeding anything it is going to require to get us to a decisive solution to cardiovascular disease or a decisive solution to cancer or Alzheimer's, the Genome Project, et cetera. It is a matter of priority, Mr. Chairman, and as a citizen and as a scientist, I think I know what the proper priority ought to be. That is the best I can do. I don't pass legislation, and I understand the constraints on you and your colleagues. I can only tell you what I know as a scientist and feel as a citizen.

Mr. PORTER. My father contracted infantile paralysis at the age of 18 months and was disabled by it physically all of his life. I often use the same example that you have mentioned as to the tremendous pay-back that has been achieved in so many different areas of science, in terms of actual savings in the economy as well as savings of lives.

I wonder if anyone else wants to comment on the same subject. I don't want to preempt.

Dr. BISHOP. I don't want to monopolize the microphone. Rather not, in fact.

Mr. PORTER. Would anyone else like to talk about that subject?

Dr. WATSON. Well, maybe I could agree with you. I don't think we want to mortgage our children's futures by just increasing the debt. I do think that we are going to have to make choices, and I, like Mike Bishop, would be personally willing to pay more taxes if it was thought that by paying more tax medical research would move ahead. And I think if you commission polls, most people would do it if they thought it was going to be well spent.

I think our responsibility as a community is is to, by working with you and others that we know that support our efforts, to try and make it clear that this is a very good use and effective use of the money. I think that is what we have to do.

ROLE OF MEDIA IN PROMOTING SCIENCE

Mr. PORTER. Dr. Watson, I think that our culture is such that most of our people get almost all of their information from television these days, and our news has, except perhaps in the case of public television, become entertainment news. We hear all the negatives all the time and we never hear the successes. And this is a sermonette I am launching into. I will be very brief. But I have been saying to Dr. Varmus and Dr. Collins and anyone who will listen that we need to find a way to get into the popular mind, the average American's mind, the importance of this kind of investment. And yes, it is important for all of you to come here and tell us, but in the end we have such a responsive government, even though people don't believe it, that what we hear from the people back home is terribly important to the choices we make here. And somehow the message of the advances of science, the savings, the potential of science to truly breakthrough and change the future is a message that we have to somehow get out of these rooms and out across the country.

We think people just inherently understand this, surely they must understand it, and yet I find increasingly they really don't understand it. They read the paper. They pick it up and they see NIH, some researcher in Pittsburgh, Pennsylvania, falsified data. This is a terrible thing. That is all they know.

They don't know what NIH is about. They only read the negatives, because that is all the popular media brings to them. And somehow we have to find a way to reach out to people with this positive message of the possibilities and the achievements of science and the fact that this is perhaps the best investment of our money of all. And that is something I just wanted to say very briefly, because I think it is so important.

Mr. Stokes.

Mr. STOKES. Thank you very much, Mr. Chairman.

My recollection, Dr. Watson, is that the first time that you and a group of Nobel laureates appeared here was in 1981.

Dr. WATSON. Yes.

Mr. STOKES. As I recall, you are probably the only one on the panel today that was here at that time with us. I think Mr. Obey, Mr. Porter and I are the only Members of the subcommittee who were on this subcommittee at that time. Mr. Porter, I might observe, was a junior Member and had just come on this subcommittee at that time.

Let me start with reference to the comment the Chairman made. While I hope he is right in terms of the fact that Congress will not cut taxes, I have to say that the matter of cutting taxes is one of the propositions in the Republican Contract With America. We have been proceeding on a 100-day course on the Contract here in the Congress. Thus far, they have passed approximately half of the items that they had promised the Nation. Therefore, I have to be mindful, and all of us who serve here have to be mindful of the fact that we have been told that they are going to pass each of the items that are set forth in that Contract.

IMPACT OF BUDGET CUTS ON RESEARCH

So that brings me to my first concern, and that is that the Contract With America, if implemented, would impose a 30 to 40 percent cut in funding for biomedical research. What impact would such a cut have on medical advances, and basic, applied and clinical research?

I am mindful, also, Dr. Watson, that when you appeared here in 1981, the NIH budget was approximately $3.5 billion. It is now approximately $11 billion in fiscal year 1995. I would assume that over this 14-year period we have seen significant advances take place as a result of the kind of investment that the Congress and the Administration have made in biomedical research. I would appreciate your comments on this matter and those from anyone else on the panel.

Dr. WATSON. Well, I first would like to mention that, of course, our budget has gone up. At the same time I think, and it was the point I wanted to make, just the inherent complexity of the human body, which is what we have to come to grips with, we have realized is just much more complicated.

Cancer is a more complicated enemy than we thought when Mike and I first met in about 1974 or 1975. I remember it was at the Airlie House that we suddenly bumped into each other, and it was one of the sort of first meetings after the War on Cancer. And we thought there would be a couple of genes out there and we would find them and, you know, we could cure it. Now there are a couple hundred. And so I think sometimes you realize you have a bigger enemy and you are going to have to have more money. I don't want to sound like a Cassandra, but I think we are going to see the enemy is a little bigger, but not a thousand times bigger. There is a limit.

We realize that we have to work equally hard these days to really see that our money is well-spent. I mean, we really have to look at how the NIH budget is spent and really say something looks good, but is doing no good. And even though it may look good to a particular place, deep down it is not doing any good. I think that is our responsibility, not only to the American people, but to ourselves. Because unless we do it, we are not going to be able to live up to the promises we would like to make.

As far as the advances, I fear that Mike Brown is right, and I should be on a drug that I don't want to take. It is an enormous advance if you just sort of figure what has happened since 1981. I think the advances have been very much in the area of heart disease. That is where the mortality has changed; that is where the collaborations with our major pharmaceutical firms, the knowledge which often goes back 30 years. And I think this is what you have to realize.

For the Mevacor, there was an awful lot of metabolism cholesterol research, which NIH supported in the 1950s and 1960s. What gave us the knowledge with which to do it, and what you have voted since 1981, is going to show up later as these drugs come out which in some cases take an awfully long time to evolve.

Phil? You seem——

Dr. SHARP. I just wanted to emphasize one thing in addition, which is that I think the resources have been well-spent. They have been competitively reviewed; it is a stringent review process. There is a lot of selection, and even though one in five is now being funded, it is being funded in a competitive way that selects quality.

But beyond the benefits of research, which are the real reasons for this NIH grant, I want you to recall that NIH is also involved as part of this research program in training the next generation of people who are going to be our physicians, research physicians, who are going to be our students and people who move out in society and generate new ideas and translate those ideas into the world and into our economy.

As the country progresses and competes internationally, our competitive position is going to be dependent upon the education and technology base of this country; by and large, a major part of it in biomedical. And therefore, NIH's investments are investments in the future economic competitiveness of this country. And if that isn't there, it will show up in very important ways.

So I think it is a very important dollar that the government spends in terms of supporting this area, and it has ramifications in direct health as well as in the status of total education in technology in the country.

Mr. STOKES. Dr. Murray?

Dr. MURRAY. Mr. Stokes, I am pleased with your question. I have often thought about it myself.

I was involved in transplantation for 20 years roughly from after World War II until 1970, and during those 20 years we were able to achieve success. And I originally was always interested mostly in facial deformities, starting from my war experience and then taking care of a lot of patients with facial cancer. So I shifted in 1970 to taking care of children with congenital deformities of the face and that is what I have been doing for the past 25 years. Now—and we were just treating them surgically and correcting the deformities. But this was getting the end-stage treatment.

But now I only wish I had another 30 or 40 years to go, because my colleagues are finding that the genetic origins of many of these deformities of the face that are transmitted are of a hereditary basis. There is a chance now of helping these children worldwide in preventing this type of deformity. So although we never dreamed 25 years ago that this was a possible spin-off, it has been. And so maybe the extra money has been in a preventive way which we really will only realize in the next generation.

Mr. STOKES. Dr. Hubel?

Dr. HUBEL. I have a couple of points to make. One is that of the money we spend to do research, I think that all of every cent of it is not necessarily wisely spent.

I remember a story that a hospital in New York decided to reconvert one of its main clinical buildings to use as a research building. And the decision was made that the operating facilities which up until that day had been used and worked fine were deemed not adequate for animal surgery in research. And this is because for some reason the Department of Agriculture controls these things.

But the effect of making animal research so expensive, having to have the most deluxe operating facilities, that sort of thing has meant that the price of a dog for Dr. Murray's research is now about $800. When I started out it was more like $10 or $15. And this has had a really disastrous effect because of really a small group of people who want to drive the costs up because they want to make research using animals prohibitively expensive. That is one example.

I have an entirely different point to make, and that has to do with what Mr. Porter talked about, the priorities of the country. I completely agree that our media, especially television, is in large part responsible for our warped priorities, not realizing that science is important, music, literature, all of things that I think the country should really concentrate on if we don't want to be thought of as Romans rather than Greeks 2,000 years from now.

But part of the problem I think is perhaps sometimes in our leadership. I was in the class of 1981 in Stockholm and that year there were about four or five Americans represented, which is more than any other single country by far. There were four or five other countries represented, and about halfway through the week of celebration, we suddenly tumbled on the fact that we were the only country that hadn't received word from the Head of State, anything by way of congratulations. And it is not that we wanted kudos. It just seemed to represent an entirely different attitude on the part of the leadership of the country concerning this.

We do get fan mail. In fact, it is a pain because you have to answer and sign these little cards. But 75 percent of the fan mail comes from other countries than this one. And again, that tells us something. If the leaders in science aren't taken seriously, and especially if the leaders in science aren't taken seriously by the leaders of the country, then something is wrong with the priorities all the way along.

I personally don't think that it would be strange or unusual to invest in the things that we prize most dearly in this country, which are things like science, literature, cultural things, things that we really want to be remembered for a few thousand years from now.

Mr. STOKES. Dr. Brown?

Dr. BROWN. Mr. Stokes, you asked what have we gotten for our money since 1981, and I think that is a very relevant and important question. We have made tremendous practical strides in certain areas. For example, the cholesterol lowering, the treatment of heart attacks with clot dissolving drugs which has reduced the mortality rate from heart attacks from around 13 percent down to between 5 and 7 percent. That is a tremendous change in our ability to save lives when people have a heart attack and go into the hospital.

We have made tremendous strides. But those strides were not based on the research that was done since 1981. Those strides which came into being since 1981 were based on the research that had been done for the 15 preceding years. So the benefits that we are going to see from the research that came from 1981, the practical benefits, we are going to see now over the next 15 years. And I think those practical benefits are going to be really astounding.

You have heard about some of them today. I think there will be further strides in the common diseases. Think about it. In 1981, we knew the genetic basis of almost no disease. There was almost no disease in which we knew exactly what was wrong with the DNA. Now, by 1995, there are several hundred dreaded diseases in which we have been able to pinpoint the defect in the DNA, some of it done by people sitting in this room.

As Mike Bishop says, there was very little known about the actual causes of cancer, how cancer was going on, what made a cell disobey the rules. Now we know an enormous amount, and there is no question that those advances will be felt in the next 15 years. Even if we stop doing research today, there is no question that we have built up enough of a knowledge base that tremendous practical implications will flow.

What we are talking about is the seed corn for the next crop. One thing that I think the Congress and the public doesn't understand is that not only has the NIH budget increased, but the pace at which research has been going has increased. The number of journals, the number of journal articles, the pace at which a scientist can get an answer to a scientific question is so rapid now, and the number of answers coming out is so fast that it is almost bewildering. We need computers. If we didn't have computers, we couldn't handle this information at all.

So the point is that the pace of research is accelerating tremendously. I mean it is geometrically accelerating. It is exploding in biology. There is no question that we will have answers to the common problems of humanity within the next decade.

And so you have to understand that the reason for the increased costs is the increased pace of science. And the promise of it is—I mean, we are getting to the point now where we have to ask, what is the final goal? I mean, what do we want? Dr. Watson says he wants to be healthy into his eighties. You know, I think that we in medicine are now getting to the point of—we are saying what is the end of it? You know, obviously we can't increase lifespan beyond a certain point.

What is the goal of all of this science? I think it is clear what our goal is. The goal is to keep everybody perfectly healthy, playing tennis, and not having pain, and not having disability until some very late time when some natural cause suddenly snuffs out life in a painless way. For the first time in the history of humanity, we are now in a point where we think that we may be able to offer that, and I am talking about real time. You know, within the next 15 to 20 years, which is hopefully early enough for some of us.

Mr. STOKES. I think Dr. Bishop has his hand up.

Dr. BISHOP. First, an obvious point that hasn't been made, the rise from $3 billion to $11 billion is in part an illusion. There is something called inflation which this body certainly knows about, and inflation is steeper in medical research for reasons that I still do not myself understand, but it is a fact that it is steeper. I hope that you will put your question to the representatives of the NIH when they are here, because I think they understand this even better than I do, and they will be able to tell you how long it has been since that rise has represented anything real in terms of resources.

Then I heard a question from you, sir, if I did, that I think deserves a direct answer. You asked, what would happen if there were a 40 percent cut in the budget. Is that correct?

Mr. STOKES. The range is a 30 to 40 percent cut.

Dr. BISHOP. Yes, sir. Again, I hope you will put that question to Dr. Varmus and his colleagues when they appear because I think they know very well.

I know in a general sense what will happen. There will be no new grants funded, period; bottom line, no new grants. People like myself will take immediate administrative cuts in our budgets, let's say in the order of 50 percent? And third, and again most important, and connected to what I said before and what others have said, I think biomedical research would essentially be eradicated as a career track for a whole generation. These young people are not stupid.

Let me tell you a story. Last year I went to lecture at Loyola High School for the second time. Loyola High School is the premier competitive high school in San Francisco which produces an astonishing number of students who go on to college and advanced study. Twice in the last five years I have had the experience of going there and lecturing to their science club, the Pre-med Club, et cetera. On both occasions the first question was, why should we become scientists, Dr. Bishop, when there is no future in that career? We know people can't get grants. We know that Congress wants to trim the budget. Fifteen years old, they have got the message. That is what I am worried about.

Mr. PORTER. It will be necessary for us to recess the hearing from 12 o'clock, which is the hour that has just arrived, to 2 o'clock. When we reconvene, we will begin the questioning at that time with Mr. Miller. This subcommittee stands in recess until 2 p.m.

[Recess.]

Mr. PORTER. The subcommittee will come to order.

The questioning will continue with Mr. Miller.

Mr. MILLER. Thank you, Mr. Chairman.

Thank you all very much for coming back this afternoon. We appreciate it. It is a pleasure just meeting you all. I want to thank you also for your presentations. I mean, this is my first time on the committee, but I understood most of your presentations. And that is very important, to have it at my level. I have been looking forward to this ever since Mr. Porter told me about this event. It is really one of the highlights.

I am disappointed that C–SPAN doesn't show up for something like this. C–SPAN will show up and listen to a Government Printing Office report for two hours; here is something important and they aren't here.

But at any rate, we will be going over this process during the next couple of weeks and we will get specifics from Dr. Varmus. You made some comments about the tough choices we are going to have, and we really are. I am a fiscal conservative. I am a former college professor, too, by the way. I have a Ph.D. in business. That is one reason you are over my head; I am in a different area of marketing and statistics.

But the tough choices we have and we are going through, whether it is basic research or—I had a group of people in my office from the Job Training Centers in Sarasota, and yesterday the community college people were in. The Head Start people were also here. I mean, where do you make your choices and how do you make sure you are getting the right end result?

IMPACT OF REGULATION ON RESEARCH COSTS

And Dr. Watson, you made the comment about making sure that we spend our money well and do good for society. How do we first of all make sure we are doing that, and where can we get more efficiencies in research? Because overall the total dollars has increased in NIH, yet both Dr. Rich from Baylor Medical School, an immunologist who spoke to us a couple of weeks ago, and Dr. Hubel mentioned the issue of dogs, referring to the issue of animals, the cost, and the issue of the audit expenses and such.

Where are areas that we can make more effective and more efficient so your dollars that can go right to the research area?

We are going through this issue of regulations today. That is what we are voting on the Floor of the House, and I think animals—I don't know too much about the animal research costs—but they have gone up dramatically, and I would be interested if you all could give as ideas and suggestions to get more bang for the buck, so to speak.

Dr. WATSON. Well, I will start in a different way. I think we took an enormous step forward with Dr. Harold Varmus as head of NIH. And Harold now has the opportunity to appoint the heads, in conjunction with the Administration, the heads of the other Institutes. And I think this is terribly important, because the whole tenor of how the money goes out can be set by the person in charge. Because you have to subtly set priorities.

To me, I am just terribly interested in who the next head of the National Institute of Mental Health will be, and I am very interested in who the head of the National Cancer Institute will be. I think the quality of the people we get in those positions will be very, very important.

Mr. MILLER. Like animals, I mean, they don't have a choice. I guess we will talk about this next week with Dr. Varmus, the standard of research animals is not within the control of the Agriculture Department. I mean, what are some areas that we could address in Congress, whether it is regulatory, or what have you, that can make your job more focused on research—which is what, you know, we want—than on regulations and satisfying some crazy Federal Government requirement that auditors are satisfied with. Maybe you can send us a report later on with some ideas.

I was just real impressed when the gentleman from Baylor made some comments about ideas on animals specifically, and he mentioned the auditing process, how many more auditors they need today than they needed 5 or 10 years ago, dotting the I's and crossing the T's are a real problem.

I don't know if anybody else wants to comment.

Dr. SHARP. I won't comment on that, because I don't believe—regulations do impact on costs slightly, but I don't believe that is the major driver. The major driver of costs in this area are people, and that you scale by people as research funds are increased or decreased.

The only thing I would add is that it is terribly important that quality remain a focal issue in this activity. Quality is maintained at NIH by peer review, competitive review, where people propose grants or programs or centers, or whatever, and then are reviewed by others in terms of competition as to which is the most qualified or the most innovative or creative. That process allows the digestion of, you know, advances in the field very rapidly. And it is one of the things that has driven forward biomedical research very rapidly in this country, as contrasted to other countries, where the system is more funded in a particular place, and then allow that to sort of substantialized over a long period of time.

Right now, peer review—a lot of young people are sitting in those sections. They have very short memories. They are looking for what can be accomplished tomorrow, and it is a very innovative and competitive mechanism to fund research. And if the world has to deal with limiting resources, then competition is the way to deal with the assurance of the quality of the program.

Dr. BISHOP. I have a thought that follows on that. I haven't studied this in detail, but I would guess that earmarking leads to substantial inefficiency of the use of research funds, because earmarking can direct substantial amounts of money to a facility, to an institution that is not competitive in the context that Phil Sharp just described. Earmarking can over endow an area, even, beyond the capacities of science to absorb the funds in a competitive way. So I would guess that earmarking can be a significant threat to getting the most bang for the buck, as you asked, because it can subvert or circumvent the competitive aspect of peer review.

I have no doubt that regulatory costs hurt us. We see that in the care of small animals, for example. One of the things that has revolutionized our ability to study disease over the last decade has been the growth of a technology that allows us to make mutations in a gene of choice in mice and other small animals. And the cost of caring for these small animals has risen at our institution by more than a factor of 10 in less than a decade. And those costs can largely be traced to the increasingly stringent demands for how these animals are housed and how they are cared for. There has to be a happy medium somewhere. I think we are way over the edge on it.

But I wouldn't venture a guess just now as to what fraction of efficiency or the inflation of medical costs accounts for, but it certainly has a large impact on the ability of young scientists to do research, because they can't command a sufficiently large budget from the competitive grant process to do that kind of research. You have to have an established reputation before you can command the kind of money that is required to do expensive animal research. So unless an institute can bail young scientists out, they are up against it in that sense.

Mr. MILLER. I am sure many of us on this committee would be interested in pursuing that. As I said, we are going through the regulatory issues which affects all areas, not just medical science. Do you have any ideas or suggestions?

Dr. BISHOP. I, for one, would be glad to—I would want to do this in a careful way. I would want to have the people who do the budgets for us and who make sure we follow the rules at my institution tell me exactly where they think there is, say, unnecessary cost, and I will be glad to do that.

Mr. MILLER. Well, you are at the frontline of the research.

Mr. Stokes, right before we recessed for lunch, commented about the possibility of a 30 or 40 percent cut. I don't want anyone to think that these are relevant numbers as far as NIH basic research is being discussed. So unless someone wants to differ with me, don't worry, those numbers aren't being talked about. That was out of line.

AGING

Let me ask one more question. You all are doing a great job in medical science of extending lives. For example, my mother-in-law who is in a nursing home is 87; my wife is an only child and her father died at age 91. They are just dying of old age. It is really very sad, she had a great life until her late 80s, and her father, he was still driving when he was 91. So you know, what do you do then? I realize this is a philosophical question.

Dr. SHARP. It is a philosophical question, but I think you hit on the issue. It is the issue that when you are 87 and you are not alert and you are not able to take care of yourself mentally, that is really where the tragedy of old age is at. All right? And I think that the need to have nursing homes and people being taken care of is primarily an issue of mental alertness. As long as you are able to be mentally alert and learn things about you, you can keep yourself engaged and take care of yourself really well.

So I think one of the major opportunities as well as major challenges facing society now is how to develop the equivalent of Lovastatin for heart disease, but in this case for delaying, not preventing, because I doubt if you can prevent it, but delaying the mental dementia that is typical of old age. Because if I had to have one—I don't mind falling over of a heart attack at 81 or 95 or 100, but I would like to be alert the moment I do it; right? Because I think it is a quality-of-life issue.

And I think there are real opportunities, particularly in terms of research and neurology and neurobiology, to have impacts on that. I had hoped that research would draw the pharmaceutical world to focus on that and given the demographics in this country that the majority of us are right behind me in the 40 to 50 in the postwar baby boom population, we are going to see enormous costs related to aging. Trying to control that by treating dementia before it comes to the stage where someone has to be put in a nursing home is a major opportunity to reduce economic costs, and where biomedical research could have an impact.

Mr. MILLER. Thank you very much.

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

I want to thank you for assembling this distinguished panel. As I mentioned to Dr. Hubel before, even though the State Department didn't respond, we sit here in awe, with admiration and gratitude for all of your contributions to the United States. Which I personally would like to thank you for and I am most appreciative.

Dr. HUBEL. I wasn't blaming the State Department, it was the head of State, that is the head of the country didn't respond.

Mrs. LOWEY. Well, I am sorry then to clarify it. I don't want to say under which Administration, but maybe we will just leave it at that. But we thank you very much.

We are very fortunate that on this committee there is very strong support for investment in the National Institutes of Health. I think we all share your firm belief that it is cost-effective to invest in NIH. By investing in research, besides saving pain and misery, we are saving dollars in the long run. Most of us in this committee are very strong supporters of the National Institutes of Health.

But I am concerned, and I wonder if perhaps we could start with Dr. Brown, because your information and findings are directly related to treatment and prevention. I guess that would go for most people on the panel. We are constantly having to make decisions in this committee and in other committees about cost savings; and you have heard the stories about the Balanced Budget Amendment and how we are going to have to cut, cut, cut.

INVESTMENTS IN RESEARCH VERSUS TREATMENT AND PREVENTION

Would you argue that we support research at the expense of treatment and prevention programs, or would you argue that we need to increase the pie, making adequate investments in research as well as treatment and prevention? I think I mentioned to you before a story I heard about recently, and we hear this over and over again. People are told their cholesterol is high, they know their cholesterol is high, but how do you modify behavior, how do you get that information out, how do you change behavior? I think this is the trick here. How do we do it? So perhaps you can comment on investment in research versus treatment and prevention, or do we expand the pie for all?

Dr. BROWN. Well, since I am a physician as well as a scientist, I think I have a foot in both of those camps. And I would obviously say that we need both in order to succeed. Research without application for treatment and prevention would be sterile; treatment and prevention without science is voodooism. So we have to have some balance between the two.

I think to simply say, well, we have accumulated so much knowledge now and what we need to do is sort of stop moving forward and go back and fill in the gaps and apply it to people, would not be the optimum thing. Because current knowledge, the knowledge that you apply may well change a year from now as our research insights become better. I would come down very heavily on the idea that we must maintain basic investments in clinical investigation with an eye toward finding new and simpler ways.

We may not need to change behavior as drastically as we think, for example, if we can find some easier way. You know, it is easier to take a pill than it is to change your diet. It is easier to take a birth control pill than it is to practice abstention. And so the fact is that science may help us in terms where we can make it less—people may have to change their lives less radically in order to ensure health if we can do better science.

Otherwise, you end up with a situation where at one moment everybody is eating high carbohydrate diets and then the next time you turn around everybody says carbohydrate is bad for you, maybe we ought to put a little bit more fat in the diet, and then somebody says vitamin A. Betacarotene was supposed to cure heart attacks, now we have a study in Finland that shows that it makes heart attacks worse.

And so if we go off trying to change behavior without enough information, we are going to have total confusion. So we need to have more science and not less science, and we need to have it tell us fairly definitively what we ought to be doing. I think a lot of the confusion comes from inadequate science and too little science rather than too much science.

Mrs. LOWEY. Well, actually, I must tell you that your response confused me completely. I would think, and I am concerned as someone who is very interested in the connection between nutrition and health, that it is troubling when one week we're told carbohydrates are "in," the next week yogurt and salads and carrots are "in". On the other hand, is the answer to pop a pill rather than changing one's diet? But then in five years you could find another reaction to those pills.

So somehow, I would rather worry about getting more information and continuing to invest in getting additional information and eat more carrots than take more pills.

Dr. Brown. Well, I think that is very rational and very reasonable. But I think one point why there is so much confusion in the public's minds about public health is that we try to make one recommendation for everybody. It is like one size fits all. We say that, for example, everybody should be on a low-salt diet because salt causes high blood pressure, and yet for many people, salt is not a threat.

We say that everybody should eat a low cholesterol diet—I say everybody should eat a low cholesterol diet, and yet I myself violate that rule because my blood cholesterol level is 150, and somehow I am genetically privileged.

My partner, Joe Goldstein, and I show a slide on our talks.

On the left side is a picture of Winston Churchill who smoked cigars, drank heavily, was always obese, and was quoted as saying the only exercise he got was acting as a pallbearer at the funeral of his friends who were joggers, and Winston Churchill lived to 91. On the other side, we showed Jim Fix who is the man who wrote a book on jogging and got everybody on the roads. Jim Fix died at 53 of a heart attack. And the question is should we all follow Winston Churchill's example or should we follow Jim Fix. Are the heart associations all wrong, are we all just wrong? Well, the answer is if you know for a fact that you have Winston Churchill's genes, then by all means, go right ahead. And if you have Jim Fix's genes, you need even more than exercise.

So we are not all the same, and something that is optimum for one person is not optimum for another person. And I think that is where our knowledge is failing. That is where we need to have more information. And it happens to be the area that is expanding and moving ahead the fastest; the understanding of genetic predisposition to disease—why one person is genetically predisposed and another one is genetically almost immune—that will tell us a lot about how to recommend an optimal life-style for everyone. So I do think we certainly agree with public education and we use the best information we have now, which is the information that I gave you about low fat diets, but we always expect that as we get better, our information may get better.

BASIC AND CLINICAL RESEARCH

Mrs. Lowey. Actually, that leads me to the next question, which was touched on before. Could you discuss the difference between basic research and clinical research, and the importance of clinical research—research on patients—to the application of your discoveries in improving health? Perhaps someone can comment on that.

Dr. Murray. I am happy to comment on that. I am not sure you can distinguish between basic and clinical research. Research is a search for truth, and there are many ways to do it.

There are some persons who will do only clinical research and never get into a laboratory, but they do systematic studies of their patients, keep good records and can produce information which will be beneficial for the health of everyone. On the other hand, you may have persons working in ventures and laboratories doing no clinical work at all and making equally important contributions to the health of society, and then you have a mixture in-between.

I think if you go back to Louis Pasteur, over 150 years, 200 years ago now, he made a statement that there is no difference between so-called basic research and so-called clinical research. And I don't know whether I can quote it exactly, but he said: They are linked together much as the fruit of a tree is to the roots. It all is bearing the fruit. So it is inquisitiveness that we need for progress.

Back to another question, or a partial answer about changing diets and all the rest. I think society, we can't change it obviously, but one of my pet peeves is diet food. We worry about obesity, and all you have to do is stop eating to some extent. You can't get the calories out of your food until it is zero, if you want you can have zero calories by not eating. And so we can't change that behavior, but we in the medical profession sometimes are blamed for the expenses of medical care. And I think that society bears some of that responsibility and blame.

Dr. BISHOP. I would guess reading between the lines that your question in part is responding to a concern that has been generated from within the medical research community. There is a general concern that the practice of clinical research, patient-based research has suffered a decline over the past decades. In part because the joy of doing fundamental research has been so large. It has been very seductive to bright young people.

I was trained as a physician, too, and I was not attracted to patient-based research. It is exceedingly difficult, it is very frustrating, you can't ask incisive questions often, it is based on large populations, there are all sorts of complications that make someone like myself turn to molecules instead.

But the community of medical science acknowledges this, and I suspect the Director of NIH could assure you that he is hearing from the community of medical science about the need to accentuate clinical research, we are not training enough people to do it, in part because there wasn't a constituency. And those of us who teach medical students, those of us who teach graduate students, those of us who try to set an example, I know a number of leading institutions that are designing deliberate programs to make patient-based research more attractive, to provide role models.

I agree, I believe there is a problem there. Pendulums swing and this pendulum swung too far and we are looking to bring it back. It takes money to do that. And I would hate to see us borrow from Peter to pay Paul. It troubles me to hear health care delivery competing solely with health research. Aren't there some other things out there that they ought to be competing with, too?

I understand the budgetary process here has become pretty constraining. I regret that deeply. But in any event, I hope that if you can find a way to avoid borrowing from Peter to pay Paul, either health care delivery, prevention as opposed to research, that you do so.

The other point is one of scale. Health care delivery just dwarfs health care research and costs. You can impoverish NIH and not have a substantial effect on the health care system. That just says that it is not a fair contrast in my mind, at least.

But in any event, we in the medical community are trying to do something about clinical research. This is not my purview, but as a senior figure at an institution that is trying to do something, I can tell you that it is on our minds, we have heard the challenge.

Mrs. LOWEY. I am hoping that working with our Chairman we can get a bigger share of the whole pie, because our difficulty is that everything in this committee is so worthwhile.

RESEARCH TRAINING

I believe my time is up. And just one last comment. I hope that we can hear from you and work with you so we can address your concerns that young people are not going into research. We are very worried about that as well. So I hope that is something that we can work with you on and come up with some good responses.

Dr. BISHOP. Well, I suspect everyone at this table, and I can speak for thousands of other scientists, we are ready to work with you. I owe an immense debt to the American public. My entire career is based on public altruism, the funds provided by the U.S. taxpayer, and that is a lifetime debt, and I would like to try to repay it however I can.

Mrs. LOWEY. I, for one, think you have done a good job, Mr. Chairman, and I thank you again for appearing here.

Mr. PORTER. Thank you, Mrs. Lowey.

Ms. Pelosi.

Ms. PELOSI. Thank you very much, Mr. Chairman.

I want to join you in expressing appreciation for the marvelous panel that you have here today. My only regret is that other responsibilities prevented me from hearing the presentations. But I have read them, and I, first of all, thank you for that and also congratulate you on the recognition that you have received for the work that you do.

I was pleased to hear Dr. Murray's response to one of Congresswoman Lowey's questions, Representative Miller, my colleague, that while we may not have the academic credentials in the same area as our witnesses, we share the inquisitiveness and the open mind and the willingness to listen and hear what you have to say and, hopefully, we can consider you an ongoing resource.

I want to also express my pride in Dr. Varmus. I know, was it Dr. Watson who mentioned that one way to make these decisions correctly is to choose the right person at NIH. And as a Representative of San Francisco in Congress, I want to also express my pride in Dr. Varmus' appointment and his fine work at NIH.

And I guess as another source of pride, I will address my first question to Dr. Bishop. You all would have been pleased to hear—I think you will recall, Mr. Chairman, when Dr. Fauci was here and one of our colleagues asked him a question about certain kinds of basic science. He responded, and then he said you will have to excuse me, but the answer I am giving you is based on the research for which Dr. Varmus received his Nobel Prize, and so here I am explaining his science, that science to you in front of him in 30 seconds or less. But in any case, we are very proud of Dr. Varmus' accomplishments, as well as those of Dr. Bishop.

In your testimony, you say that when we talk about cancer, you say the seemingly countless causes of cancer—cigarette smoke, sunlight, asbestos, chemicals, viruses and others—all these may work in a single way by playing a genetic keyboard, by damaging few of the genes in our DNA, and by damaging acceleration, getting to part of the Nobel work.

DETERMINING THE ENVIRONMENTAL CAUSES OF CANCER

Would you say—amongst some of us—and I am sorry Dr. Brown had to go, because I was really also following up on his answer before—some of the physicians in our area told women that in the case of breast cancer, for example, that some of the things that they have been told about low-fat diets and this and that are interesting and helpful, but they are not necessarily an answer to prevention in terms of breast cancer, and, obviously, it helps to have a good genetic makeup. But would you say that if we wanted to prevent breast cancer, for example, we might look more to what the environmental causes of that might be and address those causes, or are we better off spending our concentration on basic science and what has happened to the gene and when we find the answer to basic science, then extrapolate from there into what may have caused it in the environment? What should come first?

Dr. BISHOP. We don't know what causes breast cancer, that is the bottom line. And I don't know that anyone has a clear strategy as to how to find that out. So we have to take whatever clues nature hands us.

There are good epidemiologists studying populations to see whether they could find some correlation between life-style, other external factors, geographical, ethnic backgrounds, et cetera. I mean, the story that breast cancer incidence changes dramatically when, say, Japanese move to the United States, it is a very familiar story. That is a clue. It is a clue we have had for a long time. And despite some very clever epidemiologists working very hard on it, we still don't know where that clue is leading us.

So yes, we have to do clever epidemiology, and hope that it leads us somewhere. But I thought your second suggestion was actually very perceptive. You understood what I wrote.

There is a very good chance I think that as we master the genetic damage in the chemical nature of a genetic damage in breast cancer cells, that will provide us with a clue as to what is going on. Is it one cause or several, for example? What is the nature of that cause? Let me give you a tangible example.

We happen to have pretty good evidence from epidemiology that most skin cancer comes from excessive exposure to sunlight. I think that is an acceptable statement only in the last 10 years from epidemiological standpoints. And now it just happens that we know enough about the genetic damage in skin cancer cells to know that if we did not have epidemiological evidence in advance, the genetic evidence would have told us that, because the genetic damage has a chemical nature that says ultraviolet light. We can't be sure, but we can hope that a sufficiently comprehensive study of the genetic damage involved in breast cancer, about which we still know very, very little, will allow us to infer something about the nature of the causative agent or agents.

So you have to come at a problem that is so opaque at the moment from several directions. For me, the primary directions are from the bottom up, from the genes up, and from the outside in, from the epidemiology into the population.

APPLICATIONS OF AIDS RESEARCH

Ms. PELOSI. I appreciate that. Thank you, Dr. Bishop.

To all of our witnesses, I wanted to ask you a question about the budget for 1996. Dr. Varmus says that it is a budget which reflects scientific opportunity in a number of areas. One of these—since our colleagues have raised the issue of why we spend so much on AIDS research, I wanted to ask you that question in a little bit of a different way.

Why do you think AIDS research is important, what do you think we can learn from it about other diseases and causes of illness because of damage to the immune system, if I may just open that question up to the table.

Dr. BISHOP. Well, I am dominating the microphone here. I don't like that.

Phil, you go first. But I have some ideas.

Dr. SHARP. One, this is still an emerging problem in this country, and we still don't know the full ramifications of having this virus as a new agent creating disease in the society. So though we have been studying it as a community for 10 years or so, it is apparently a new virus in man and a new virus in this society, and we are gaining some appreciation for the difficulty of trying to control the virus and cure a patient of it. But there are new hopes as new drugs are coming out of Merck primarily, and other companies, that are protease inhibitors and can be used to treat it.

Now, there are going to be multiple ramifications beyond just the AIDS virus. The approach that now seems most promising is developing protease inhibitors which are compounds that will inhibit a protease inherent to the replication of the AIDS virus. If that actually works, and there are reasons to suspect it will—every virus I know of has as a critical part of its replication cycle a similar protease-type maturing step. If we can design chemical agents that would inhibit AIDS virus, we will be able to design probably similar chemistry, similar way agents that might inhibit herpes viruses and other infectious viruses that are major pathogens, disease-causers.

So we are going to gain something from the focus on this virus in terms of just technology development in how to control viruses. It is an immunodeficiency virus, it destroys our immune system, and as we understand how it destroys our immune system, then we will have a greater understanding of how to intervene in immunity, and autoimmune diseases is on the order of 5 percent of the total population. I mean, it is probably the area I expect cell biology and modern biomedicine to have the biggest impact on in the next few years.

And then beyond that, the molecular biology of this virus, as I illustrated in my comments, involves numerous processes inherent to the biology of the cell. And by focusing on those molecular processes, not only do I hope to be able to learn something about how one could intervene and try to control that virus, but also these cellular processes. The third thing I would say is that gene therapy holds one of the major hopes, I think, in actually treating long-term people, and I expect that gene therapy would also be an approach to controlling the HIV virus.

So I think the research has ramifications beyond just its single focus on HIV.

Ms. PELOSI. Thank you very much, Dr. Sharp.

Dr. BISHOP. He stole my thunder.

Ms. PELOSI. Imagine that.

Dr. BISHOP. I can't imagine it. I think there is a point worth emphasizing here.

I can't imagine that in the United States there is an educated parent today who sent their children off to college without thinking of AIDS. I certainly did when I sent my two sons to college. This is by way of saying that I—there is great concern that what we see at the moment is but the tip of an iceberg as to what this plague could become. It is rampant in Africa, it is growing in Asia at an absolutely terrifying rate.

I think it would be a human arrogance of a very large order to assume that this disease will of necessity remain restricted to the specialized populations that it presently afflicts in the United States. We would be fools not to be working full out on this thing until we understand it, how to cure it and more importantly, how to prevent it, without any other rationalization, spin-off, whatever, although they are going to come, as Phil said.

Ms. PELOSI. Thank you very much, Dr. Bishop, Dr. Sharp, all of you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Istook.

Mr. ISTOOK. Thank you, Mr. Chairman.

Gentlemen, very pleased to have you here. I just want to make one personal note first.

Dr. Watson, I read your book "Double Helix" several years ago before I knew that I would be on this subcommittee, and I very much enjoyed your account there. The one that really ought to be here today is my wife, who is a registered nurse. Her love for medicine is such that back when she was going through nursing school and already was a surgical technician for a couple of years, she used to work as a volunteer for a couple of thoracic surgeons, just scrubbing in on surgeries and assisting in that way, just because of her love for doing so. So I wish she were here to meet you gentlemen.

I really only would have one question, but I think it ought to be a difficult one, realizing the funding questions that confront this Congress, the debt that is being passed on to future generations, the need for prioritizing things, and frankly, for making many people unhappy in the process of doing so.

RESEARCH PRIORITIES

What I would like to ask each of you on the panel is if you could only fund—and I have to be restrictive by the nature of the question—but if you could only fund two areas of medical research—I expect Dr. Watson would certainly say the Human Genome Project, maybe you wouldn't. I will let you speak for yourself. But if you could only fund two areas, two focal points of medical research, I would like to know what your individual priorities are in that respect.

Dr. WATSON. Well, I will start out.

Dr. BISHOP. Here, Jim. I want to hear this.

Mr. ISTOOK. Please don't try to sneak three or four in. I realize that it is human nature to do so, but I am really trying to get an indication of what people see as priorities, both in the sense of need and in the sense of where breakthroughs might be most attainable. Whatever criteria you use.

Dr. WATSON. Well, in my case, I certainly would fund cancer research. It reflects what I have been involved with for 25 years. We have learned an enormous amount, and I think we are going to have real payoffs, but we need more pure science, and so I am terribly excited about where we can go in curing some real cancers.

Second, I would go after mental disease. I have a son who has one, and so I speak as a parent. And our knowledge base is abysmal. We, you know, we need a wall for the brain.

Mr. ISTOOK. You are speaking, I presume, of the physiological aspects, as opposed to just psychiatry itself?

Dr. WATSON. Forget psychiatry. I think the great evils of this world were Marxist in thought, if you want to know—if you want to have my attitude.

Mr. ISTOOK. Some people were taking note of that.

Dr. WATSON. I would like to understand human behavior, because it is with young people, and it is just a tragedy in my family. So that is my feeling.

Mr. ISTOOK. Certainly. Thank you.

Dr. Sharp.

Dr. SHARP. It is very hard, but I will answer your question.

Mr. ISTOOK. It is meant to be hard.

Dr. SHARP. It is hardy, because it is hard to pull the fabric of biological science apart and to say that this is that area, and that is that area, because they do crossover. And in that regard, and not to repeat Jim's necessarily, I would say that if you had to focus, you have to focus on the basic. You've got to have general medical science. This system is still so unknown that if you can't push the horizons forward in a fundamental way, you are never going to make progress on anything.

Mr. ISTOOK. What do you mean by general medical science?

Dr. SHARP. The division, meaning there is general support of basic biological processes, and the understanding of how those processes work. And there is an Institute at NIH called General Medical Science that supports that type of research, it is not in heart disease, it is not in mental health, it is not in others.

And then I will speak for the other side, and again, emphasizing that you can't pull the fabric of it apart, but I think from a societal cost point of view and benefit and quality of life, as Jim said, mental health is some place we have got to invest more dollars, because we are going to invest a heck of a lot of more medical dollars in that area. So if we can't intervene and control the rate at which we have dementia in society, we are going to see ourselves being swamped by the problem. And I think that is a very important area.

Dr. MURRAY. Well, the question is unanswerable in any meaningful way, but I will answer. But I would like to emphasize that whatever research or investigation, it should be at the very basic level. To give you one group I would study, I would pick on congenital deformities that are universal, and I think it has been estimated at half a billion in the world population today. And it deals with children, it deals with family, and I would sort of mobilize all of the resources of genetics, nutrition, environment and try to get to the bottom of that.

The reason your question is impossible to answer is that the best—or the most important decision any scientist makes is the selection of the problem. And one wishes to select a problem that is solvable, but how do you know it is solvable—well, you just don't. But you have certain intuitions. And speaking personally, after World War II, somehow it seemed to me that the problem of transplanting of organs seemed reasonable. There were hints from patient care, from research of others all over the world that it seemed solvable in this particular time.

Now, to get a success required the merging of many different kinds of sciences, both clinical and basic. But from my own point of view, nothing can be more satisfying than to create or to make a patient's health return, to restore a patient to health. And so to solve the problem of transplantation which we haven't solved, but we were able to bypass, we called on many different resources.

Now, if you asked this question to me 40 years ago, I think I wouldn't have said study renal function, but one has to go back to a basic science to merge and try to produce the finished fabric. And I am going to just add something because I know you are from Oklahoma City, a place that I am very familiar with. One of our sons and daughters-in-law were married in Edmond, and the patients I have up here as an exhibit, the two in the middle, are from a town about 50 miles east of Oklahoma City. She is the world's longest-living renal transplant, it happened in 1956, and she has had children and grandchildren and all the rest. So there is no way that we could have predicted 40 years ago that we could produce this now.

So your question is a good one, but it is unanswerable.

Mr. ISTOOK. Thank you.

Dr. BISHOP. My answer will resemble Dr. Sharp's, but more extreme. It is based on what I think is the guiding principle of how science succeeds. It succeeds through the opportunism of sciences, the geniuses of great scientists to be able to recognize when something is ready to be solved, when something is accessible.

So I would argue that we would no longer have the luxury of earmarking one or another disease, one or another human ailment for a particular study. I would argue that we would have to simply say, there is a pot of money for the best biomedical fundamental scientists to compete for, and their genius for following the answerable problems to the end would be what drove the directions in which research went.

I would have another pot of money for patient-based research that would again allow those best scientists to compete in order to pursue the avenues that they perceive and can document are solvable. I think it would be unwise to designate money to a particular disease problem under the severe circumstances, and instead, I would want to exploit this driving principle of science.

It succeeds through opportunism. So we would be led gradually to success in various areas of basic science that would play out in success of various areas of clinical research. I wouldn't want to resort to that, but that is the best thing to do in the circumstances you describe.

Mr. ISTOOK. If I understand you correctly, basically you are saying that the solution with the limited resources, you think that rather than line-iteming—this is what we are going to spend on this division of NIH or some other aspect of medical research—you would like to see Congress make the pot of money available and then have—I presume Dr. Varmus would say through NIH, but anyway, the point is through scientific——

Dr. BISHOP. I would say so, too.

Mr. ISTOOK. And then let the allocation of the funds be made from there.

Dr. BISHOP. Strictly competitive, absolutely, based on the best ideas, the best prospects for success and let the creativity of individuals—that is what drives success in basic science. That is why we have always been able to argue so successfully, that money spent on cancer has benefits to heart disease and vice versa. So I would just take those labels off, and I would extend that to patient-based research as well.

Mr. ISTOOK. In essence, you would delegate the answer to my question to the NIH.

Dr. BISHOP. I would delegate the answer to your question to the driving genius and perception of the scientific community and it would be very competitive under these circumstances, it would be Darwinian, to say the least.

Mr. ISTOOK. Would you expand on that for me? How do you see that would change the motivations of researchers compared to what the motivations are under the existing system?

Dr. BISHOP. I doubt that it would change the motivations very much.

Mr. ISTOOK. I mean, I realize they have motivation to get the answer to the question.

Dr. BISHOP. I think it would change motivations very little. But what it might do, and I made this point this morning in your absence, it would become quite Darwinian, because you are implying that there are much less funds than now available. What I think it should do first and foremost would be to essentially shut down biomedical research as a career track for the next generation. They are going to walk away, the youngsters who are 15, 17, 18, looking at a career prospect under those circumstances will find something else to do. We talked about this in some detail this morning. I think that would be the most dramatic and long-lasting impact of such extreme measure.

Mr. ISTOOK. Do you think there would be no young persons attracted into the research fields or do you think there would be a screening process regarding who sought——

Dr. BISHOP. I fear, although I can't document this, but the really smart ones would be the ones who would go somewhere else and find something else to do.

Mr. ISTOOK. I guess I misunderstand, because I thought you were advocating the use of the pot-of-money approach, but then you are saying that you think that it would mean people would not want to enter the field.

Dr. BISHOP. I think that if you could——

Mr. ISTOOK. I don't think that is what you intend to advocate.

Dr. BISHOP. I don't want to advocate that, no. But I was trying to make two points. One, that under the circumstances you articulated, it would be foolish to try to choose one or two particular areas to emphasize, for reasons I gave, and reasons that you heard from others as well. We would be better off under those circumstances to allow the opportunistic and creative drive of scientists to drive the application of funds, because that is probably the best way to utilize a limited amount of money.

But on the other hand, I fear that you will drive away a great deal of talent, because the implication is there will be very limited resources.

Mr. ISTOOK. So what you are talking about is that the limitation on resources would be what would generate the problem you foresee with driving people away, not the system or its allocation?

Dr. BISHOP. The severe limitation of resources, yes.

Mr. ISTOOK. Thank you.

Dr. Hubel.

Dr. HUBEL. Well, I agree with what Dr. Bishop has just said, but I think it is in a way a little bit like ducking the question, which was if you had to choose two areas. And so I am going to take the question seriously.

Mr. ISTOOK. Thank you.

Dr. HUBEL. Just as an exercise perhaps for myself. I would certainly choose molecular biology and genes, genetics as a field. That would include cancer. So it is a bigger, it is a bigger field. I think anybody nowadays in biology would be crazy not to keep an investment in that, and in fact, further that with all their might.

The main area that I would choose—you can call it special pleading—is my area. That is, studying the brain. And when I say studying the brain, I include emphatically the psychiatry that you mentioned and all of that, because I think all of that depends on the brain.

If we understand the brain, we will understand almost everything in psychiatry and maybe everything, including the neuroses, the psychoses that I think we are coming slowly to an understanding of, schizophrenia and manic depressive psychosis, polar—whatever they call it nowadays. When I was a medical student, those things were thought to arise from maltreatment or unfortunate upbringing when you were two years old. Nobody thinks that any longer. So if we don't understand completely those two conditions, we certainly are a lot closer to it.

But I think understanding the brain will not only give us some obvious things, like solutions to multiple sclerosis, Alzheimer's disease, Parkinson's disease and all of that, but it will help us understand how to educate our children, for instance, because if we try to understand how people learn, without understanding basically how it happens, that is understanding the brain, we are sort of speculating in a void. It can only help. The same is true, obviously, of deviant behavior of all sorts. That depends on the brain in large part. I don't see how one can lose in investing heavily in that whole area.

I should add maybe that advances in brain science, even in the restricted sense of curing disease of the brain, shouldn't be thought of as limiting itself to old age and having the effect simply of making us older, because it has to include all sorts of malformations of the brain, mental retardation, dyslexia, multiple sclerosis, things that occur in youth and in young adulthood. So it embraces all ages, it embraces every walk of life.

In addition to all that, as if that weren't enough, I think the same arguments could be used to support studies of the brain as are used to study the universe. Astronomy gets a fair amount of money and it isn't curing any disease whatsoever, as far as I know, and it isn't having any practical applications, at least darn few. But it still justifiably deserves our support, because it is an intellectual adventure that we are able to engage in suddenly. I am thinking now of brain studies. We have the equipment to go ahead with it and to be remembered a couple of thousand years from now.

So those are the two areas that I would choose, if I had to.

Mr. ISTOOK. I appreciate it.

Thank you very much, gentlemen.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Istook.

A few comments, if I may.

First, this subcommittee does not earmark. Although we appropriate by Institute, and although the other body on occasion has been known to earmark, I will tell the Members of my subcommittee that if they propose an amendment to earmark, it will be ruled out of order. We simply believe that decision is for science and not for politics.

Second, another comment. There is a group of people in the United States that probably are the strongest lobby of all; they make the NRA look weak by comparison, and that is the animal welfare people. There is a whole group of people in this country that care a lot more about animals than they do about human beings, as a matter of fact. They are the ones that drive the changes in regulations by which you have to live, and there is some good I think that comes out of that. One is that we are, I think, learning to use computer simulations wherever possible instead of animals, and where that works as well, and yet we realize what a cost that puts upon research.

The third thing I want to comment on is, that when I think of Winston Churchill, I also think that he sealed all the windows in the houses that he lived in because he thought fresh air was bad for you. So, I think of more than just his genes cheating the Grim Reaper in the face of a terrible life-style and a terrible environment.

Isn't there also recognized, even by science, a certain something else in terms of longevity and living, and that is the zest for life, the purpose, the will to—he was a man for all seasons, with so many interests and intellectual challenges that he met into the last years of his life. Isn't this also part of good health, too, and isn't that what we are perhaps talking about when we talk about mental health and its importance?

Mr. Miller has gone down to vote; I am hopeful he is going to come back so we can continue the hearing; if not, we will have to take a very brief break and then we will go back through.

CHANGES IN HEALTH CARE DELIVERY

I wanted to ask you about the change in the practice of medicine. We are right now undergoing in this country a huge change in how medical services are delivered to people. The fee-for-service medicine that has been the hallmark of our country for a very long, long time is giving way, it seems to me, very rapidly to the model of HMO, where services are provided at some form of capitation and where the impetus is to treat as efficiently as possible to serve the bottom line.

How is that likely, if at all, to affect biomedical research? Is there any effect that you see in terms of delivery that will work back up the line toward what biomedical research does, what you look at, how you conduct research?

Dr. Bishop?

Dr. BISHOP. Well, I don't think what I am going to say will be news to anyone on the Hill because of the intensive activities last year that were made by various medical institutions. Most medical research and teaching institutions have subsidized their research efforts out of their clinical income. That is a given; that is widely admitted, and it was a way of making up the difference between what research costs and what has been available from the Federal Government. For fundamental scientists, such as myself, this benefit is indirect; that is to say, there is no doubt that clinical income has been used to renovate basic laboratories at medical schools, but few, if any, basic scientists at my institution at least derive direct research support from that. More frequently, it is clinical research, patient-based research, research within clinical departments that has been subsidized from clinical income.

There is the additional difficulty that, in the past, it has been possible to get reimbursement for patients on clinical protocols at the level of cost, and obviously when you turn to a completely market-controlled economy, you are not going to find an insurance company anymore that is interested in reimbursing for costs related to clinical research, hospitalizations necessitated by the research protocol rather than by the care of the patient.

So in a nutshell, that is the circumstance, as I understand it. This is not in my immediate purview, but I have certainly heard about it until—well, to the point of saturation from my dean and my colleagues in clinical medicine.

Mr. PORTER. It is going to be necessary to take a very brief recess. We will return as soon as Mr. Miller returns.

The committee will stand in recess.

[Recess.]

Mr. MILLER [presiding]. We are going to get started, if we can. I get to have my chance for a minute to ask some more questions. I am thoroughly enjoying this.

Dr. BISHOP. So are we.

Mr. MILLER. So often the hearings are not the experience that we are having today, so I sincerely appreciate you all coming today.

TRENDS IN NIH FUNDING AND GRANTS AWARDED

As you know, we are going to have some very tough choices when we talk about budgeting for job training, education, military and all of these issues. How do you divide up a limited amount of money, how do you control items like Medicare spending? When you get down to the question of basic research, how much money is enough money?

Now, you mentioned that within the grant process 80 percent of applications get rejected. At NIH, about how many apply; also there is more money available, isn't there? NIH has grown dramatically in the past 10 years, but yet you are saying more people are being rejected in grants.

So my question is, are you saying that it is harder to get grants, but yet there is more money in the pie, the pie is getting bigger? Is it because there are more people applying out there or is it just because there are more good projects out there?

Another question is, do you see diminishing returns on your research money? This is true on any project. For example in environmental, when you try to restore a piece of land to the original pristine condition, the last few percentage points are not as effective.

When do we know that we have enough money? You claim that it is so hard to get grants and this deters the younger scientists coming up, yet there is a bigger pie.

Dr. BISHOP. Well, part of the bigger pie is consumed by inflation, certainly over the last 10 years. I don't have the numbers at immediate hand, but part of it is inflation. And then as Dr. Brown emphasized, there has been a staggering expansion of our success, and you wouldn't like to constrain that success. You would like to sustain it.

Mr. PORTER. Are there more people——

Dr. BISHOP. Yes, there are more people in biomedical science now than at any time in the past. Again, I couldn't give you the exact demographics. But there are more people.

You asked what is enough money? The experienced observers of the NIH granting system, people who have watched the quality of grants over the years, usually settle on a number of, say, about 30 percent. If you could fund 30 percent of the truly acceptable grants, that this is probably about right in terms of not excluding anything that is truly worthwhile, credible, outstanding, but just arbitrarily gets excluded the way it does now when the limits range from 10 to 20 percent.

Mr. MILLER. Thirty percent, is that——

Dr. BISHOP. From my own experience in peer review, I would be comfortable with that number, yes. When I was doing peer review some years ago—for four years I was on the study section and for two years then I was the chair—the funding levels ranged down to 50 percent. I felt that we were funding some things which were acceptable science, might well be worthwhile, but if push came to shove, the Nation could do without. But when you get below 30 percent, you start making arbitrary choices that are truly crippling.

Mr. MILLER. We are at 20 percent?

Dr. BISHOP. It depends on the Institute and the month, or the budgeting period; 10 to 20, depending on the Institute.

Mr. MILLER. Do you have a comment, Dr. Sharp?

Dr. SHARP. I don't disagree with what Mike says—quite the contrary, I support it. But I argue that it isn't an issue of how many people are entitled to be supported in terms of new grants, it is what is the money doing for the country and society.

And then you look at the investment that has been made in biomedical research, and you look at our health industry and health costs, you look at biotechnology, you look at agriculture, where the science of the gene has changed how we do or think about the future of agricultural products. You look at the environment and you look at remediation of the environment and impact on the environment, and at economic issues. All of this turns around biological science, biomedical science in a fundamental way. So this investment by society underpins all that. So how much, it is hard to say.

There are really very exciting opportunities out there. And the more that you can support, I believe in time, you will reap benefits from it in multiples on that investment. So it is very hard for the community to say, this is enough or this is not enough. It is just that there are opportunities and they are important beyond just simply the specific disease or specific thing being commented on at any particular moment. And it is a good investment for society, in that it serves society in a fundamental way, in an economic way.

There are not many ways that society is going to be able to expand. This is one area in which advances in science are translatable into products, into treatment, into other ways of improving the quality of life, and that is still true, that some day it has to become not true. But at this stage, it is still true.

Mr. MILLER. I would like to counter that this new Speaker, although I haven't talked to him specifically about this, but he is a big believer in basic research. I think you would find the Speaker feeling very strongly about research, like he feels about the Library of Congress. He likes to talk about how the whole gene therapy programs of the year 2000 are going to be very different and offer such great potential. So I think you will find support from our side of the aisle.

SCIENTIFIC PRIORITIES

Continuing on the same question from Ms. Pelosi and Mr. Istook's comments, it raises the question of AIDS research versus cancer research. This is part of the politics. And it has been raised at these meetings, "Well, we are spending too much money on AIDS and not enough on cancer." In total amount of dollars we are spending more on cancer, but then we have breast cancer and prostate cancer and all of the different cancers.

How do you reconcile those decisions and those allocations? You hate the politics-playing, and certainly that shouldn't be part of what we are earmarking, and I am new to this committee, but I already see that playing out here.

Dr. WATSON. I came before this committee to talk about money for AIDS, I think it was in 1986. We were genuinely scared, not because we were part of any minority group, but we were worried that our children were going to be growing up and we didn't know how infectious the virus was.

We are still not sure that it won't get worse, because of mutation, and I think the AIDS thing came on from, it struck younger people early in life. So we saw people who we trained to be successful and they were cut down early in life. So it was partly the age, and I think it was partly the infectious nature.

If it had been a little worse, we would have been afraid to go into restaurants. And so far, you know, you could say it has been terrible for some people; it hasn't been quite as bad as our worse scenarios, but I think I would hate to say that we are spending too much money on it.

I was at a hearing where a woman came in and said, you are not spending very much on Parkinson's disease. I certainly agree. And I think it reflects the nature of the problem. I will come back to it.

You were asking how to pay for it. I have a simple solution, that is we are now making it possible to live into our 70s, we should delay Social Security benefits, delay a few of these things. If people are healthy, why shouldn't they work? And maybe they won't go so often to Florida, but you know——

Dr. SHARP. That is the wrong statement, Jim.

Dr. WATSON. I am just saying is that we can't go on giving a good life to people who aren't working. So we are going to have to really see this whole entitlement program—I am about to be 67. I would hope that I wouldn't have to receive any entitlements until I am 80. I don't really see why I should. And so I think we do have that, which as a Nation it is going to be expensive, any way you look at it.

Mr. MILLER. Do we politicize money too much? You have obviously dealt with this more than I have.

Dr. WATSON. No, that is the game. I mean, you have to.

Mr. MILLER. It is coming up this year, we could talk about breast cancer, we could talk about sickle cell, or we could talk about diabetes. You don't sense we are politicizing it? I don't know. Have you seen it in the past?

Dr. WATSON. We are political animals. I don't object to it. I think we have two great defense needs, you know, from our country to keep someone from dumping a nuclear weapon on us that we don't want, and it is certainly very scary. It is also very scary to think that you might have a stroke, or particularly scary if you have had one.

Mr. MILLER. Alzheimer's is the one that——

Dr. WATSON. So I do think in the sense of absolute priorities, there isn't anything really more important than our health. And it is a question of whether the money we are spending is good for the dollar, compared to other ways the government is spending money. We are all prejudiced here at the table.

Mr. MILLER. We have so many other questions about defense dollars. By the way, the Social Security age is being raised. It is already in the law to raise it to 67.

Dr. WATSON. Oh, we should be going higher than that.

Mr. MILLER. But it is already built into the law to go to 67.

Dr. BISHOP. Your question about what is enough reminded me of a simple formulation that I find useful in talking to the general public about this issue. I guess simple arguments aren't foreign to this Hill, so I will use one here.

The research and development effort of the United States defense industry is usually about 10 to 15 percent of its total budget. The pharmaceutical industry spends on the order of 9 to 12 percent of its annual budget on research and development. The health care industry, if you will, of the United States or the United States health care system, at this point, I guess, is down to around 1 percent of its annual budget going to research and development. So in all fairness, those numbers suggest to me that some reordering of priorities might be wise. It seems to me we are a bit low in health care research in terms of those simple budgetary reckonings.

And I think the politization of funding to which you alluded is driven by the sense that there isn't enough to go around. There was much less of it when I was younger. Mary Lasker had a very famous statement: People don't die of immunology. It was her way of explaining to scientists why it was necessary to appeal for money for cancer or for AIDS or whatever. But it was possible in those days to appeal for money for cancer without robbing Peter to pay Paul. In other words, more money was put into cancer, but that money didn't come out of rheumatoid arthritis or multiple sclerosis or Alzheimer's, or whatever. Now, that is what is happening.

Mr. MILLER. Thank you.

I see Dr. Hubel has something to say.

Dr. HUBEL. Something is bothering me, and it occurs to me because of your question about the pot getting somewhat larger with time, as it has, and yet the numbers of grants being funded has gone from 80 percent, or whatever it started out as, down to 20, or whatever it is now. I think part of this is built into the system of training in a way that I don't pretend to have the answer for, but maybe some of my colleagues do.

In molecular biology especially, if an investigator who is in full pelt producing doesn't have six or seven graduate students, and the number may be much larger for all I know, there is something wrong. And six or seven graduate students at any one time, if it takes four years to get your Ph.D., that means you might train 30 or 40 people in a lifetime in the scientific lifetime. If each person in academia trains 30 or 40 people, I don't think it is any wonder that the rate of funding of our grants is declining. We are just training a whole lot of people, partly because certain kinds of science depend on person power, if I may use that term. And you just can't make a go of the sort of slogging work that goes on in a lot of molecular biology without hands, and that is the way the system seems to me to work.

I am in a completely different field. We have one, roughly, graduate student at any one time, because we can't delegate our work. We have to do our own experiments. So it works in a very different way. But we are a real minority, I think, when it comes to the way biology works. We have an absolute explosion in the number of people who are looking for jobs, and it is going only to get worse unless something changes. So I think that is a problem we all have. So I can understand your puzzlement.

Mr. MILLER. Thank you.

Mr. PORTER [resuming]. Thank you, Mr. Miller.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

We have enjoyed very much the kind of testimony that you have given here today. I think it has made all of us have a great deal of pride in the type of achievements the medical and scientific profession has accomplished over the years. As a member of this subcommittee, I am proud to have been a part of providing the kind of funding that has made these types of accomplishments possible.

RESEARCH ON MINORITY HEALTH

However, one of my greatest concerns is that while we talk about the significant breakthroughs in terms of medical science and the quality of medical care that is now available to Americans, the increased longevity, and so forth, we must recognize that a significant part of the American population has not had the benefit of many of these medical breakthroughs. I speak significantly of the African-American community and other minority groups.

In 1985, the DHHS, then the Department of Health, Education and Welfare (HEW), under Secretary Heckler conducted a yearlong study on the disparity between white and minority health in America. At the end of that year, we learned that there were 60,000 excess deaths in the minority community per year. We also learned that black Americans die eight years earlier than whites; and that in all of the diseases—cancer, heart attack, stroke, cardiovascular disease, and diabetes—that there is a wide health disparity between the majority of Americans who suffer from those diseases and minorities who suffer from them.

I would just like to take advantage of having you gentlemen, who are preeminent in your field, talk about how we can arrive at the point where all Americans can have parity in the way that diseases affect them. It seems to me that these breakthroughs ought to benefit all Americans. And, in that vein, I would pose to you specifically the question of whether it ought not be the National Institutes of Health, our most preeminent scientific institution and probably the best in the world, that takes the lead in the fight to close this health disparity gap between white and black Americans.

I would appreciate any comments that you may care to make.

Dr. BISHOP. Well, the National Institutes of Health, of course, is devoted to research, fundamental research and clinical research. And to the extent that there are biological explanations for differences in disease among different ethnic groups, I think the NIH can help there.

But the issue of scale came up a while ago. I personally believe that the problem of which you speak arises primarily from the inequities of health care delivery in the United States. It arises from inequities in education, it arises from inequities of all sorts that are socioeconomic in origin; much more than it arises from inequities in fundamental research.

You could take the entire budget of NIH tomorrow and devote it to health care delivery, and I don't believe you could solve the problem that you spoke of. I think that problem has to be solved in how America delivers health care. And that, of course, is not something I am an expert in. I am a private citizen. I have my own opinions about it. I think the way we do it now is a disgrace.

It could be orders of magnitude better—inequity in quality, et cetera. But NIH was not conceived and, in my view, is not funded and nowhere in its mission is health care delivery mentioned. It should, of course, and does do research on health care delivery, on outcomes of different kinds of treatment, on comparisons of populations. That is part of the NIH mission. But to deliver health care to the American public in an equitable manner, that is something that I think far transcends the NIH budget and far transcends the NIH mission.

Mr. STOKES. Can I just follow up on that point. If NIH's mission, as we discussed and you testified earlier this morning, is to try and find out what causes cancer and to create a cure for cancer, as we also discussed this morning, are you now saying that if while you are trying to cure cancer, that if for some reason or other you find that African Americans are prone to have more cancer than white Americans, that that doesn't fall within the scope of NIH's research?

Dr. BISHOP. Oh, to do the research required to demonstrate that point, of course. But to react to it within the universe of health care delivery, of getting proper health care, say, to black Americans, that is something that I can't say NIH can handle.

Mr. STOKES. Let me rephrase my question. It just seems to me that, fundamentally, this type of disparity exists. If you are trying to find out, as Dr. Brown talked about this morning, how we arrive at the point that some day we will be able to totally eliminate the cholesterol problem, and yet we know at the same time that African-Americans suffer from greater blood pressure, higher heart attack risk, things of this sort, shouldn't NIH in the biomedical sense be ascertaining the basic reasons why this disparity exists?

Dr. BISHOP. Absolutely. Yes. I would say that is certainly part of the mission. That is a problem that biomedical research can and should address, yes.

Mr. STOKES. That is what I was trying to get at.

Dr. Watson, after you give your reponse, then the others can follow.

Dr. WATSON. I am not sure I saw accurate figures, but it was on mortality differences between black and Caucasian populations. The great difference occurs if you look at life expectancy from birth, but if we were the same age and you compared your life expectancy versus mine, it wouldn't be very much difference. So if you survive to 60 years old, whether you are black or white, you are probably going to live roughly the same time. It is the very early years—these were the figures I saw.

Dr. SHARP. I don't think they are quite true.

Mr. STOKES. No, they are different figures than what I have seen.

Dr. WATSON. I have seen some of them, but I think there is a great deal in early mortality which is social, is probably distinct from biological. I am just trying to—environmental, if you want for——

Mr. STOKES. The latest statistics indicate that black Americans, particularly males, die approximately somewhere between 7.1 to 8 years earlier than their counterparts, in the range of 60 to 70 years of age. There is an interesting phenomenon, and that is—for those who reach 80 years of age and beyond, then black Americans tend to outlive white Americans. That is a phenomena that no one has yet been able to explain.

Dr. BISHOP. Our assumption, for example, hypertension, high blood pressure, there is no—my very first patient with high blood pressure was a young black man who died of the disease under my care, and I have known ever since then that this is a special problem. It is a problem of greater intensity for the black than the white. I can see just now some hope that the genetic research that is proceeding and being fueled, in particular by the genome effort, is going to lead to an explanation for that, and therefore perhaps to a solution. It may take a generation, but I can see it. We are beginning to understand the genetic predispositions to high blood pressure in animal models, and I think it is only a matter of time before we will be able to map that out in humans as well. That is NIH's mission, absolutely.

Mr. STOKES. Thank you very much.

I appreciate it, gentlemen.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

ENVIRONMENTAL RESEARCH

Dr. Bishop, you talked at the very beginning about damage to genes, and part of that damage is undoubtedly environmental, but we may not know how much. Are we spending enough money on environmental research to determine what role that plays in disease? If you look at the figures for the National Institute of Environmental Health Sciences, you see that it has not increased nearly at the rate of all of the other Institutes.

Dr. BISHOP. I would suggest, first of all, that we have or will shortly learn as much about the contribution of the environment to cancer from mapping out the kinds of genetic damage that lead to cancer as we have learned from epidemiology, and most of that genetic research was not funded under the rubric of environmental research, under the rubric of that Institute.

I hasten to add that I have the highest regard for that Institute. I think the sorts of things they are charged with are extremely important. I would be reluctant to answer your question about whether we are spending enough money. I really am not sufficiently well informed. But I would like to emphasize that we are learning about the environmental contributions to cancer from different vantage points, and they can't be restricted to a particular Institute.

I would also like to emphasize that it is not at all yet—it depends on how you define environment. If diet is environment, yes. If the contributions of humankind to our environment are what you define as environment, then I think the jury is largely out, except in special cases; high-intensity exposures in industry. But for the general public, whether it is something beyond diet that is responsible for breast cancer or something beyond diet that is responsible for colon cancer, I think the jury is very definitely out. And we would be best to have many irons in the fire, rather than just one iron labeled environmental research.

Anyone else?

SCIENTIFIC OPPORTUNITIES

Mr. PORTER. Let me follow up on a question we had started to discuss earlier. About the time when we began to seemed to get a much better fix on a number of diseases, along came the AIDS epidemic, an entirely new disease, or at least apparently an entirely new disease. And the question comes to mind as to whether we can ever catch up. As we unlock the secrets, will that always be one that is ahead of us with something new to cope with, or do you feel that we are outrunning the potentials out there with a real chance of unlocking all of the keys?

Dr. SHARP. I think everyone would have an answer to that, probably very similar. Yes, there will always be new problems. AIDS will not be the last infectious disease this country sees, particularly as populations in the world increases and world travel becomes more and more common and cheap and inexpensive.

But there is no question of the fact that the quality of life now of our citizenry is much better than it was, you know, 20 years ago. Infectious disease in mid-life is almost nonexistent as a killer in major parts of the population. We talked about polio, we have talked about a number of things. The biggest growing population in the country is over 100 years old. This is a success story; this is not wring your hands, we have got problems we can't deal with. This is a success story.

We are living better and longer, and with less fear and more confidence and a higher quality of life than we have ever lived before. And, hopefully, we can extend it to all of our citizens and, hopefully, go on and improve it. But I think it would be a mistake for the community and its representatives and the press to give the impression that we haven't made solid progress over the last 20 or 40 years in terms of biomedical research.

Dr. BISHOP. But I sensed some intellectual play in your question, and I want to respond to you, and it goes as follows: people like E.O. Wilson and others who study ecology have made the point that we have identified about a million species of multi-sited organisms in the world and there must be at least 8, 10 million.

So we have just scratched the surface of identified species. And this man, E.O. Wilson, he is one of the great giants of that field. And at the end of his autobiography he says that if he were starting over again, he would no longer work on a large scale; he would restrict himself to a square foot of ground, because he believes that the challenge of identifying the unknown species of microbes is every bit as large as the challenge of identifying the unknown species of multicellular organisms. So the answer to your question is, you bet, there is a long way to go. There is a lot out there we haven't dreamed of, I am sure, as a microbiologist I say that.

Dr. HUBEL. I might also say, though, I don't think we would have a chance in the world of ever solving AIDS, or even being able to address the problem, were it not for what we know now about molecular biology that we didn't know 20, 30 years ago. And as more diseases come along like AIDS, if they are not to swallow us up, and if AIDS were spread by infection the way a cold is, we might go to the same fate as the elm has gone with the Dutch elm disease. If we don't prepare ourselves by learning as much as we can about the way the very most basic processes in biology work, we are running a big risk. It seems to me that part of this is insurance.

Mr. PORTER. Staying ahead.

ROLE OF NIH FUNDING

Let me go back and ask each of you what role a grant or funding from NIH played. Very briefly, in each of your cases, did it play a role in your initial research?

Everybody is saying yes.

Dr. WATSON. No. I am too old for that. Actually, I had a fellowship when I found the "Double Helix" from the National Foundation for Infantile Paralysis, so it was essentially the desire to cure polio, with the feeling that you wanted a broad base of science knowledge and, fortunately, they interpreted it broadly, and so I had that funding.

Later, NIH was totally vital for a period when I ran a lab at Harvard University, between, essentially, 1956 and 1972, where we did make some very major contributions to our knowledge of how genes function. So without NIH and without the expansion that it offered, I wouldn't have succeeded. And I should say that I guess I am proud of a number of my students, but particularly of the student Mario Capecci, who has changed the world of higher cell biology by this wonderful technique called gene knock-out. You can just knock out the gene and find out what it does to a mouse, and that is very, very important now in trying to understand the human genome. You know, his whole career was NIH.

PRIVATE SECTOR RESEARCH

Mr. PORTER. What would you say to those who would say well, industry provides more or approximately half of the research money spent on medical and related R&D in the United States today, and we don't really need NIH. You can rely upon industry or academia or foundations, perhaps, to fund research. What would you say to people who believe that?

Dr. SHARP. The industry funds in total numbers, U.S. industry, about the same as NIH in terms of health care. It is about the same. Of that number, 90 percent, 80 percent, depending on which one of the pharmaceutical industries you will talk to, is in development, and that is funding clinical trials which are highly expensive in-stage development of a product, and then secondary funding, expanding uses. Not a criticism. That is their business. They do it remarkably well. And academic institutions cannot do that at all. There is no way an academic institution can maintain the focus, expertise, diversity to do that.

They also invest in drug discovery, but almost every drug the pharmaceutical industry develops is in license in some part of its technology, if not in the initial product itself. So they depend on the biomedical community, NIH and other sources, to raise the wealth of knowledge in fields that then they are able to develop in terms of specific pharmaceutical products. Much of that technology is in license. And all of the biotechnology products I mentioned in my presentation, which are now in biotechnical firms and served by large firms, were in license.

Now, the issue in health and in biomedical research is a little different than that of the semiconductor, because there, that is a technology issue. As you probably gained from the conversation today, the level of basic knowledge in this field is one in which there is a revolution going on. And particularly a human-related revolution in terms of knowledge.

And this has got to be supported in a diverse geographical and institutional way. There is no way you would want to turn the Human Genome Project over to a pharmaceutical company, all right? You just don't want it. Because if it was done, no one would trust it; all sorts of things would happen. So NIH support of technology and knowledge in this area and development has been essential for development of that. You ask anyone in the pharmaceutical world, they will tell you that.

And the way the technology transfer has developed in this country, it has worked very well in moving technology from NIH-supported research into private sector companies. And we are better at it than any other country in the world and we have benefited more from this research than any other country in the world.

U.S. RESEARCH COMPARED TO OTHER COUNTRIES

Mr. PORTER. How would you compare our public and private research to that of other countries? Are we far ahead of all others?

Dr. SHARP. I think I would answer that question differently in different ways. I was interested in Jim's comment and wanted him to mention the fact that his work was done in England, in 1953 when that work was done, the focus of molecular biology, the great strengths of it were in England, and was transplanted here by the training of people there to this part of the world, and has grown here. It still remains a strong community in England. Given scale of size for the European countries, I don't think they are quite scaled in size as strong as we are now in molecular and cell biology. Part of that is cultural.

Some countries are having a heck of a time teaming with genetic engineering and recombinant DNA as a concept. Whereas this country, after the public discussion of it in the 1970s, has dealt with it and trusted private and public organizations to develop genetic engineering and use it as a practical science, and we are working through those things in a very public way.

You look to Asia, you see Japan now making major advances in biomedical and biological research. You are beginning to see the same develop in the other Asian countries, who are further back in technology, but coming forward.

So there is a general understanding that this type of technology, as I mentioned before, is a technology that is going to underwrite many activities in the future. Not only in health, but in other parts of the industrial sector, and there are major investments being made there. I think we are premier in the world scale right now, and I believe that is a position we want to keep.

Mr. PORTER. Dr. Hubel.

Dr. HUBEL. In my field, it is not only a question of being premier, but as I said before, we are far ahead of all of the other countries in the world put together in brain research. England used to be the foremost country in this area. I think my generalization, and it may be too broad, is a combination of the animal rights movement and Mrs. Thatcher have put an end to that. And so it is done. And what makes me terrified is that it could be over and done with here, if the surgery that is coming, that we foresee coming, is too radical.

In Japan, there may be three people working on the brain in the whole country, as opposed to 300 in this country. The numbers don't tell everything, but they certainly tell a whole lot.

One of the things I admire most about the support system in this country is the wonderful symbiosis between the universities and the support organization. The way the universities benefit from the research that is done, which is, except for a certain institutions, most of it is done certainly in universities.

Our university system, thank heaven, is so much better, for example, than Japan and Germany's, that we can sort of thank our lucky stars from a point of view of competitors, that they don't have universities of the sort that we do. The combination of the RO–1, the Individual Investigator Research Grant, and the ability to carry it out at the university has really been tremendous in this country.

My own research had been supported originally for three years by Walter Reed, where I got my start, but from then on, it has been almost entirely the NIH, with some support occasionally from the Navy and from the Air Force. But no question about where it all came from.

CLOSING REMARKS

Mr. PORTER. Let me say in closing that I think most Members of the subcommittee realize what a treasure NIH is to this country and to the world, that we don't want to lose young investigators, that we don't want to lose momentum in biomedical research, that we want to take advantage of the tremendous opportunities there are, and it seems to us that so many things are so much closer than they were just a short time ago, and that we want to give biomedical research the tools that it needs to succeed.

We take our responsibility regarding the budget very seriously, obviously, but we were sent here to determine what are the priorities for spending in our country, and to determine what is essential and what is not essential, what can be delayed and what cannot be delayed. And I believe that if the message is heard very loudly and strongly in our society of what has and can be accomplished, that as a priority, biomedical research will stand at the very top of the list. The question is whether that message is being heard or not.

I can't tell you how much we appreciate all of you coming here this morning and this afternoon, all day to testify before us. After hearing Dr. Sharp I will revise my estimate; your students did miss you, and greatly.

In the end, Dr. Hubel, you talked about radical surgery, and I worry about radical surgery here, too. But I sit here and say to myself, weren't the founders of this country wise people who put together a system that is extremely deliberative, extremely participatory, and one that is slow.

It takes a long time to make decisions, and the likelihood of their being very radical in the end is much reduced. And so the process that we are in now in looking at budget priorities, I think, has profound implications for many, many different things, but among them, certainly biomedical research. And, hopefully, as a result of the process and participation in it and the sending of the messages of the value of biomedical research, in the end the decisions will be good ones and sound ones and we will put it in the priority where it deserves to be.

In any case, all the Members of the subcommittee appreciate very much your coming here. Someone said earlier this is the highlight of our year, and it truly is. And we have learned, I think, a great deal from you and we are in your debt.

Thank you all very, very much.

Dr. BISHOP. Thank you.

Mr. PORTER. The subcommittee will recess until 10 a.m. tomorrow.

TUESDAY, MARCH 14, 1995.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. HAROLD VARMUS, DIRECTOR

DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR

DR. WENDY BALDWIN, DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH

DR. MICHAEL GOTTESMAN, DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH

DARYL CHAMBLEE, ACTING DEPUTY DIRECTOR FOR SCIENCE POLICY AND TECHNOLOGY TRANSFER

FRANCINE LITTLE, DIRECTOR, OFFICE OF FINANCIAL MANAGEMENT

DR. WILLIAM PAUL, DIRECTOR, OFFICE OF AIDS RESEARCH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. The subcommittee will come to order.

Let me begin by apologizing for my voice, which normally is not sounding like this, but, as a result of a very bad cold——

Mr. VARMUS. We can help you with that.

Mr. PORTER. You have a cure for everything.

We are delighted to welcome this morning Dr. Harold Varmus, Director of the National Institutes of Health. As we begin six days of hearings, I think we will have very stimulating testimony on each of the Institutes following Dr. Varmus' opening statement this morning.

You, obviously, come before us at a very challenging time. Congress has committed itself to bringing the budget into balance and to re-examining every area of government expenditures. Dr. Varmus, I am very pleased that your statement addresses many of the questions being raised as we undertake this re-examination, and you argue very persuasively for the health and economic benefits that are the direct consequences of NIH research.

Some predict gloom and doom for biomedical research spending in the years ahead. I have said that every sector of our government must bear its fair share of the burden in deficit reduction. I am also very confident that the Congress will look at priorities and will understand the value of biomedical research to the people of our country and, indeed, to all humankind.

We look forward to your testimony this morning and of the Directors of the individual Institutes over the next few days. We welcome you here and are delighted to be able to spend the next few hours with you.

Dr. Varmus, if you would like to proceed.

INTRODUCTION OF WITNESSES

Dr. VARMUS. If I may introduce my colleagues here with me. Immediately to my left Dr. Ruth Kirschstein, Deputy Director, you know well; Dr. Wendy Baldwin, Deputy Director for Extramural Research; Daryl Chamblee, Acting Deputy Director, Science Policy and Technology Transfer.

Starting from my right, Ms. Francine Little, who is the Director of the Office of Financial Management; Dr. William Paul, who is the Director of the Office of AIDS Research; Dr. Michael Gottesman, who is the Director of the Intramural Research Program; and Mr. Dennis Williams from the Department of Health and Human Services (DHHS).

OPENING STATEMENT

Mr. Chairman, I am pleased to present to you the President's 1996 budget for the NIH. As you know, the President proposes to increase our budget of last year by $467 million. It is a 4.1 percent increase above our previous appropriation of $11.306 billion. That is an increase which will allow us to keep pace with the inflationary rate for biomedical research and development and will allow us to continue to make progress against a wide variety of diseases.

The proposal maintains our basic activities in many ways and it also emphasizes the Administration goals, goals to work on breast cancer, AIDS, the health of women and minorities, high performance computing, and tuberculosis.

In addition, our budget request also highlights a number of scientific opportunities that have been identified by NIH as components of our program that we hope to provide especially strong support for in the coming year. That includes enterprises that will convert our recent discoveries in neuroscience, cell biology, and genetics into advances against diseases of the brain, the reproductive system, connective tissues, and certain cancers.

We will emphasize prevention strategies through a better understanding of infectious agents, immunization, and behavior. We will develop novel therapies that are based on gene transfer to ailing cells and drug design guided by our understanding of molecular structures.

Our emphasis will allow us to invest in infrastructure through shared istrumentation, development of DNA sequencing techniques, and a limited construction program. And, finally, with modest funds we will augment the efficiency of our research and administrative operations with a modern communication infrastructure.

These requests reflect the commitments of Secretary Shalala and President Clinton to fundamental research and human welfare and it also embodies their conviction that an investment in biomedical science yields large dividends for the Nation's health, its economy, and its traditional values.

Now, as you have yourself said in your opening statement, I am bringing this budget proposal to you in unusual times. The Administration and the Congress are attempting to control budget deficits and the national debt through restrictions on Federal spending and on the size of agencies. These restrictions, of course, place unusual demands upon those of us who head such agencies to defend them in an especially forceful way. It is my conviction the NIH is particularly well positioned to do that. I base my belief on our ability to defend our agency's activities on, first, a long history of scientific accomplishment and documented progress against disease; on the diverse economic benefits of our research, which I will outline for you in just a moment; on the stringent review mechanisms that we have in place each year to guarantee that we are setting proper priorities and funding the best science that our investigators propose; on our international stature that allows American biomedical research to stand at the forefront of the world's activities; on our education and training programs; and on the popularity of our major goal, the improvement of human health through scientific research.

Now, as you know, Mr. Chairman, the economic benefits of our work are sometimes overlooked, but they warrant special mention here in view of current debates over government support of scientific research. Let me mention just four areas in which the economic benefits have been most palpable.

First, our research programs directly create skilled jobs, both in NIH-supported laboratories and in many U.S. companies that supply the materials and the instruments that are used in such research. This is an industry which is sometimes overlooked, but it is a very important industry that helps to provide a positive trade balance in our country, and supplies reagents all over the world.

Second, our activities help to maintain the vitality of our academic institutions—universities and private research institutions—that are the envy of the world and have consequences in many fields of inquiry, including many fields that are required for leadership in science, technology, and industry.

Third, the knowledge that we generate through NIH-supported research is essential for many of America's most successful businesses and technological enterprises. This is most obvious to all of us through the activities of the pharmaceutical and biotechnology industries that depend directly on basic biomedical sciences to develop drugs and other products. But it is less widely appreciated that NIH-initiated research has profound influences in many other of our industrial enterprises: medical forensics, where DNA typing is now commonly used to identify suspects; in agriculture, where genetically altered plants and animals are improving yields and extending shelf life and cutting costs; in manufacturing, where genetically engineered enzymes are revolutionizing the production of many chemicals; in environmental sciences, where modified soil and biophysical methods are inexpensively restoring soil and water to their natural states after contamination. And NIH affects a variety of other academic fields—from ethnology to linguistics and other areas, such as anthropology. You will hear from our Institute and Center Directors over the course of the next two weeks about how our knowledge gets transferred into a wide variety of disciplines.

Fourth, our research often produces major economic benefits when it helps to prevent, to control, and to reverse disease. The Nation has been caught up in a debate over delivery of health care in part because of the dramatic increases in the costs of care, and

I would argue that many of those increases have occurred for reasons that are unrelated to NIH-based research. And the savings provided by our discoveries are often overlooked. Many of those advances reduce expensive hospitalizations, eliminate the need for costly procedures, and increase the productivity of our citizens. And again you will hear many examples from such advances from the Institute and center directors.

Let me mention a couple of examples that come from the past.

The use of psychoactive drugs, such as lithium for manic-depressive disorders, drastically reduces hospitalization for mental illness, saving the country at least $7 billion a year and restores many patients with mental illnesses to productive lives.

The recent discovery over the last several years of Helicobacter pylori, a bacterial cause of gastric ulcer and possibly of gastric cancer, allows cheaper and more effective therapy for gastric ulcers and reduces expenditures each year by at least $400 million. There are other examples in the statement, which I am submitting for the record.

Now, such successes that we have had over the past 20, 30, 40 years are traditional sources of pride and they have paid the investment in our agency many times over. But I remain especially proud of our capacity to return to this table every year with new successes. Let me mention just briefly a few of them. You will hear many of them mentioned again by Institute and Center directors.

In the area of cancer genes, as is well-known, in the past year NIH-supported science has led to the isolation of the BRCA–1 gene, a breast cancer gene, and also to a number of other genes that are implicated in colon cancer, melanoma, and kidney cancer. These findings presage a revolution in the cancer risk assessment and a deeper understanding of how cancer arises.

We have had a major breakthrough in the treatment of sickle cell disease. The use of a simple drug, hydroxyurea, alters the composition of hemoglobin and thereby reduces the number of sickle cell crises, which cause so much pain and hospitalization for these patients, by about 50 percent.

The so-called PEPI study has led to a demonstration that hormone replacement in post menopausal women lowers indicators of cardiac disease, and will likely be shown to reduce cardiovascular disease as well.

We have had the first drug in many years that is effective in the treatment of alcoholism, naltrexone, a drug which happens to be described in today's Health Section of the Washington Post.

We have a new vaccine for whooping cough that has proven to be safe as well as effective in recently completed trials.

We have a drug that can be given through an ocular implant to prevent blindness from cytomegalovirus infections in AIDS patients.

Investigators, supported by the NIH, have found a naturally occurring peptide, called angiostatin, that inhibits the metastatic growth of tumor cells and offers a new strategy for cancer therapy.

The so-called obesity gene governing appetite, weight gain, and diabetes in mice offers new possibilities in the control of nutrition and metabolic disorders.

The antiviral drug, AZT, has been shown to prevent transmission of HIV from infected women to newborn infants.

And we will describe a wide variety of discoveries in basic science during the course of the next few weeks.

Let me say a word or two about the tempo of our research.

Two weeks ago, your committee heard the testimony of six American Nobel Laureates, each of whom told a personal story of scientific insight. In each of those stories you heard how, over the course of decades, each of their fundamental discoveries has advanced our understanding of cancer, heart disease, the brain, the immune system, and the human genome, and how some of these discoveries have contributed directly to the Nation's health through transplantation surgery, through biotechnology, and through drug development.

The stories that you heard are useful reminders of the deliberate tempo of biomedical research and the collaborative efforts required to convert discoveries to practical benefit. Viewed in the context of that hearing, we can see how the discoveries I have just mentioned to you, this year's discoveries, are either clinical developments with a rich history of basic science behind them or fundamental discoveries that may have a complex future of clinical application before them.

I want to mention a couple of additional examples to illustrate that point.

As you heard from the Nobel Laureate, Michael Brown, the pharmaceutical industry's study of drugs known to lower cholesterol can reduce mortality by more than 40 percent in patients who have preexisting coronary artery disease. Now, these extraordinary drugs, which have now been tested in large field studies by a number of pharmaceutical companies were developed by private industry only after NIH-supported scientists did a number of things. Our investigators established that the cholesterol levels in the blood are strong predictors of coronary artery disease; they outlined pathways for synthesis, metabolism, and the bodily traffic of cholesterol; and they pinpointed an appropriate enzymatic target for the development of drugs.

The second example concerns a material called thrombopoietin. The biotechnology industry announced this year the isolation of a factor that stimulates the growth of platelets, a material which will soon be available to reverse one of the most devastating effects of chemotherapy in cancer patients, the bleeding caused by platelet deficiency. This will reduce both the morbidity and the hospital costs for cancer patients. The isolation of this factor by the biotechnology industry only became possible in the last couple of years because we had two decades of earlier research on cancer viruses in animals and factors required for the production of other blood cells.

One last example: protease inhibitors. As you heard recently, AIDS researchers have been heartened by evidence that the so-called "protease inhibitors" appear to be the most effective and least toxic drugs yet available for the treatment of HIV. These drugs are directed against so-called protein-chopping enzymes, or proteases, that were discovered about 20 years ago using retroviruses of chickens and mice and then, more recently, studied with HIV. Basic research, largely supported by the NIH, was required to show that these enzymes are essential for the virus, to delineate their molecular structure, and to define their relationship with enzymes that are found in other viruses and in normal cells. With this information in hand the pharmaceutical firms sought and identified the inhibitors now being tested in patients.

Now, as you and your committee well know, Mr. Chairman, the world is in the midst of a revolutionary phase of biological research when genes and cells and complex phenomenon are being understood at an unprecedented rate. Our budget places emphasis on several areas of research, reflecting enthusiasm for these fields and our conviction that judicious investments can produce important health and economic benefits for the public.

At the same time, we have to recognize that the prospects for capturing these clinical benefits of our new knowledge are threatened—by the Nation's financial straits, by the deterioration of the scientific infrastructure, and by the tensions created within the scientific community generated by intense competition for support.

The past successes in biomedical research that I have outlined for you have depended upon well-trained scientists, a vibrant network of academic and government laboratories, innovative pharmaceutical and biotech industries receptive to the findings of NIH-supported science, and sustained support of research by the Federal Government, largely through the NIH.

Despite present fiscal circumstances, the Administration has made a commitment with its budget to continue such support. I ask that the Congress join the Administration to help us to continue to pursue our traditional objectives, health through science.

Thank you and I will be happy to answer any questions you or your fellow Members might have.

[The prepared statement and biography of Dr. Harold Varmus follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institutes of Health

Mr. Chairman, Committee Members:

I am Harold Varmus, the Director of the National Institutes of Health, and I am pleased to present to your Committee the President's FY 1996 budget for the NIH.

An overview of the FY 96 budget for the NIH

The President proposes to increase the NIH budget by $467 million, or 4.1%, above the FY 1995 appropriation of $11.306 billion, keeping pace with inflation in biomedical research and allowing us to continue making progress against heart disease, cancer, AIDS, mental illness, and many other maladies.

The proposal emphasizes the Administration's goals to promote research on breast cancer, AIDS, the health of women and minorities, tuberculosis, and high performance computing. The request also highlights emerging scientific opportunities we at NIH have identified as components of our program that warrant especially strong support. If the President's request is appropriated by the Congress, we will be able to proceed with enhanced vigor to convert recent discoveries in neuroscience, cell biology, and genetics into advances against diseases of the brain, the reproductive system, and connective tissues, as well as several forms of cancer. We foresee new means to prevent disease through a better understanding of infectious agents, immunization, and behavior, and we anticipate the development of novel therapies for the next century, based on delivery of genes to ailing cells and drug design guided by molecular structures. We can also enhance our ability to pursue these and other goals by investing in shared instrumentation, DNA sequencing technology, and a limited construction program. In addition, we will augment the efficiency of our research and administrative operations with a modern communications infrastructure.

I believe that this budget request reflects the commitment of President Clinton and Secretary Shalala to fundamental research and human welfare. It also embodies their conviction that an investment in biomedical science yields large dividends for the nation's health, its economy, and its cultural values.

The value of the NIH to the nation

I bring this budget proposal to you in unusual times, when the Administration and the Congress are attempting to control budget deficits and the national debt through restrictions on Federal spending and the size of Federal agencies. These strictures demand that agencies justify their budgetary requests in especially forceful ways. I believe that the NIH is particularly well-suited to do this, based on its long history of scientific accomplishment and progress against disease, the diverse economic benefits of its research, its stringent review mechanisms, its international stature, the education and training it promotes, and the popularity of our major goal: the improvement of human health through scientific research.

The NIH invests in diverse programs that have major public benefits and are essential to a competitive nation in an increasingly technological world. We support health-promoting research conducted by our intramural program and at nearly 2000 of our country's colleges, universities, and other scientific institutions, and educational programs that provide information about health to the public and train many of the nation's outstanding young scientists. To do these things, we have harnessed a broad range of scientific talent, including basic biological and clinical scientists, chemists, applied physicists, computer scientists, behavioral scientists, and epidemiologists.

Our agency has pursued its goals with remarkable success for over fifty years. This success can be measured in several ways: by America's unequivocal world dominance in biomedical science; by the unremitting stream of exciting scientific discoveries supported by the NIH; by many improvements in health through the prevention and treatment of disease; by the strength of our research-intensive universities, which are the envy of the world; and by direct and indirect economic benefits of NIH-sponsored research.

The economic consequences of NIH research

The economic benefits of our work are sometimes underappreciated, but they warrant special mention in view of the current debates over government support of scientific research:

(1) Our research programs directly create skilled jobs, both in NIH-supported laboratories and in the many U.S. companies that provide the materials and instruments used in research. Stimulated by a strong research environment, these companies have become international leaders and favorably influence the balance of trade.

(2) We help to maintain the vitality of the academic institutions in which NIH-sponsored work is done----a vitality that has consequences in many fields of inquiry important to America's leadership in science, technology, and industry.

(3) The knowledge generated by NIH-supported research is essential for many of America's most successful business and technological enterprises. These effects are most obvious in the pharmaceutical and biotechnology industries, which depend upon discoveries in basic biomedical sciences to develop drugs and other products. It is less widely appreciated that NIH-initiated research profoundly influences many fields other than health: medical forensics (where DNA typing is now commonly used to identify suspects); agriculture (where genetically-altered plants and animals are improving yields, cutting costs, and extending the shelf life of common foods); manufacturing (where genetically-engineered enzymes are revolutionizing the production of many chemicals); and

environmental sciences (where modified bacteria and biophysical methods are inexpensively restoring soil and water to their natural states after industrial contamination).

(4) NIH research often produces major economic benefits when it helps to prevent, control, or reverse disease. Because the nation's expenditures for health care have risen dramatically over the past decade, largely for reasons unrelated to NIH-based research, the savings provided by our discoveries are often overlooked. Many advances reduce expensive hospitalizations, eliminate the need for costly procedures, and increase the productivity of our citizens:

* Fluoridation saves the country approximately $4.5 billion each year by preventing dental caries;

* Psychoactive drugs---lithium for manic-depressive psychosis, clozapine for schizophrenia--- drastically reduce hospitalization for mental illness, saving over $7 billion per year, and allow patients to return to productive lives;

* Vaccines provide enormous savings through the prevention of infectious diseases; for example, a new vaccine against Hemophilus influenza type B will save the nation over $400 million each year by preventing meningitis and consequent mental retardation;

* The recent discovery of Helicobacter pylori, a bacterial cause of gastric ulcer, allows cheaper and more effective therapy with antibiotics, reducing expenditures by over $400 million each year; and

* The control of blood lipid levels and other preventive measures have reduced the death rates for two of our three most common lethal diseases, cardiovascular disease and stroke, by nearly half, producing enormous effects on the cost of care and the health of our citizens.

Recent accomplishments by the NIH

Such successes, Mr. Chairman, are traditional sources of pride for the NIH, and they have paid for the total investment in our agency several times over. But we are equally proud of our capacity to return to this Committee each year with an impressive collection of new successes, such as the following list of some of our fundamental discoveries and clinical advances from the past year:

* Presaging a revolution in cancer risk assessment, the long-sought gene for some hereditary breast cancers, BRCA-1, has been isolated, as have genes that predispose some patients to colon cancer, melanoma, and kidney cancer;

* A simple drug, hydroxyurea, alters the composition of hemoglobin and thereby reduces by half the painful crises that commonly hospitalize patients with sickle cell disease;

* Hormone replacement successfully controls blood lipids in post-menopausal women and likely reduces cardiovascular disease;

* Naltrexone is the first drug in many years to help in the treatment of alcoholism;

* A new acellular vaccine for whooping cough is safe as well as effective;

* Ocular implants of the drug gancyclovir are effective means to prevent blindness from cytomegalovirus infections in AIDS patients;

* A naturally occurring peptide, angiostatin, inhibits metastatic growth of tumor cells by blocking blood vessel growth, offering a new strategy for cancer therapy;

* The so-called obesity gene, which governs appetite, weight gain, and diabetes in mice, has been isolated from mice and humans;

* The anti-viral drug, AZT, can prevent transmission of HIV from infected women to newborn infants; and

* Many new discoveries have been made about the biochemical mechanisms that control cell growth and cell death; the detailed shapes of important molecules, large and small; the functions of the immune system; and the patterns of development of several complex organisms.

The tempo of development of NIH research

Two weeks ago, this Committee heard the testimony of six American Nobel Laureates, each of whom recounted a personal history of scientific insight. Over the course of decades, each of their discoveries has advanced our understanding of cancer, heart disease, the brain, the immune system, or the human genome, and some have contributed directly to the nation's health through transplantation surgery, biotechnology, and drug development.

This year's catalog of progress at the NIH also ranges from fundamental science to specific therapeutic and preventive strategies. The stories told by the Laureates are useful reminders of the deliberate tempo of biomedical progress and of the collaborative efforts required to convert discoveries to practical benefit. Thus each of this year's advances has either a rich history of science behind it or a complex future of clinical application before it. Three examples of recent success illustrate both the pace and the partnership necessary for progress:

(1) Cholesterol reduction. Company-sponsored studies of drugs known to lower cholesterol levels have recently revealed that these drugs reduce mortality by more than 40% in patients with pre-existing coronary artery disease. These extraordinary drugs were sought and developed by private industry only after NIH-supported scientists established that blood cholesterol levels are strong predictors of coronary heart disease; discovered the pathways for synthesis, metabolism and bodily traffic of cholesterol; and pinpointed an appropriate enzymatic target for drug action.

(2) Thrombopoietin. During the past year, the biotechnology industry announced the isolation of a factor (thrombopoietin) that stimulates the production of human blood platelets. This breakthrough means that it will soon be possible to reverse one of the most devastating effects of chemotherapy---the bleeding caused by platelet deficiency---and thereby reduce morbidity and hospital costs for cancer patients. Isolation of the platelet factor became possible a few years ago thanks to basic research that fortuitously identified a related gene in a virus that causes leukemia in mice. The work also benefitted from many years of NIH-supported research experience with other factors required for production of blood cells.

(3) Protease inhibitors. Last month, AIDS researchers were heartened by evidence that the so-called "protease inhibitors" appear to be the most effective and least toxic drugs yet available to combat HIV. The protein-chopping enzymes (proteases) that serve as targets for these drugs were first discovered using retroviruses of chickens and mice and then, more recently, studied with HIV. Basic research, largely supported by the NIH, proved that the proteases are essential for retrovirus growth, uncovered the molecular structure of the enzymes, and defined their relationship to proteases found in other viruses and in normal cells. With this information, pharmaceutical firms sought and identified the inhibitors that are now being tested in patients.

A commitment to the future

The world is in the midst of a revolutionary phase of biological research, when genes, cells, and complex phenomena are being understood at an unprecedented rate. The emphasis our budget proposal places on several areas of research---including neurobiology, cell biology, virology, genetics, and developmental biology---reflects our enthusiasm for these fields and our conviction that judicious investments can produce important benefits for the public---progress against cancer and diseases of the brain and other tissues---over the course of the next several years. At the same time, we must recognize that the prospects for capturing the clinical benefits of our new knowledge are threatened by the nation's financial straits, by the deterioration of the scientific infrastructure, and by the tensions created in the scientific community by intense competition for support.

Past and future successes in biomedical science depend on well-trained scientists, a vibrant network of academic and government laboratories, innovative pharmaceutical and biotech industries, and, most importantly, sustained support of research by the Federal government, largely through the NIH. Despite current fiscal circumstances, the Administration has made a commitment to continue such support with the budget I am presenting to you today. We ask that the Congress join the Administration to help us continue to pursue our traditional objective---health through science.

I will be pleased to answer any questions you might have.

HAROLD E. VARMUS, M.D.

Director
National Institutes of Health

Dr. Harold Varmus was sworn in as the Director of the National Institutes of Health (NIH) on November 23, 1993. Dr. Varmus is the first Nobel Laureate to serve as Director of NIH. He was previously a professor of microbiology, biochemistry, and biophysics, and the American Cancer Society Professor of Molecular Virology at the University of California, San Francisco (UCSF). He is an internationally recognized authority on retroviruses and the genetic basis of cancer.

Dr. Varmus and his UCSF colleague, J. Michael Bishop, M.D., shared a Nobel prize in Physiology or Medicine in 1989 for demonstrating that cancer genes (oncogenes) can arise from normal cellular genes, called proto-oncogenes.

In recent years, his work has assumed special relevance to AIDS, through a focus on biochemical properties of HIV, and to breast cancer, through investigation of mammary tumors in mice. His research activities have been supported by grants from the NIH, by his professorship from the American Cancer Society, and by the Melanie Bronfman Award for Breast Cancer.

Dr. Varmus has served as Chairman of the Board of Biology for the National Research Council, an advisor to the Congressional Caucus for Biomedical Research, a member of the Joint Steering Committee for Public Policy of Biomedical Societies, and co-chairman of the New Delegation for Biomedical Research, a coalition of leaders in the biomedical community. He directed "Winding Your Way Through DNA," a popular public symposium on recombinant DNA staged by UCSF last fall.

The author or editor of four books and over 300 scientific papers, Dr. Varmus has been elected to the Institute of Medicine, the National Academy of Sciences, and the American Academy of Arts and Sciences. His most recent book, "Genes and the Biology of Cancer," intended for a general audience, was co-authored with Robert Weinberg for the Scientific American Library. He was an editor for several professional journals, and has served on a variety of review and advisory boards for government, biotechnology firms, and pharmaceutical companies. In 1986, he chaired the subcommittee of the International Committee on the Taxonomy of Viruses that gave the AIDS virus its name HIV.

Dr. Varmus was born December 18, 1939. He attended public schools in Freeport, Long Island, N.Y. His father (Frank) practiced family medicine, and his mother (Beatrice) was a psychiatric social worker. He is a graduate of Amherst College (B.A. 1961), where he majored in English Literature; Harvard University (M.A. in English Literature, 1962); and Columbia University (M.D. 1966). While at medical school, he worked for three months at a mission hospital in northern India.

After an internship and residency in internal medicine at Columbia-Presbyterian Hospital in New York, Dr. Varmus served as clinical associate for two years at the National Institute of Arthritis and Metabolic Diseases in Bethesda, Md.

Dr. Varmus went to UCSF as a postdoctoral fellow in Dr. Bishop's laboratory in 1970, initiating a longstanding collaboration to study tumor viruses, and was appointed to the faculty later that year. He became a full professor in 1979 and an American Cancer Society Research Professor in 1984.

Mr. PORTER. We want to thank you for your excellent statement.

DECREASE IN NIH BUDGET—PROJECTIONS THROUGH FY 2000

Obviously, we are pleased to see that NIH received a $467 million increase in the President's 1996 budget request, but we notice that for 1997 the request drops by more than $350 million and that by the year 2000 NIH funding would be $1 billion below your 1996 request, and this in a President's budget that does not bring the budget into balance by 2002, in fact continues $200 billion deficits.

So our first question is, why has the Administration taken this roller coaster approach to NIH funding with severe long-range cuts? Please describe for us the impact these cuts would have on your priority research programs and investigator success rates.

Dr. VARMUS. Yes, thank you. First of all, Mr. Chairman, the predictions for the outyears that were outlined in this year's budget have been responded to by the Secretary of HHS in the following way. She has pointed out that her Department will take such reductions but that she has yet to determine whether they will be applied evenly among the agencies. As she has indicated in her testimony here, she is prepared to try to protect our investment in the NIH and that she has not determined as yet how those reductions will be applied across the various agencies.

This being said, let me attempt to answer your question about how these reductions would affect our success rates in succeeding years.

First of all, as you know, we have a number of variables in our budget. An important one in considering how to answer your question is the degree to which we follow the principles of cost management.

About four years ago your committee, in response to a crisis in the success rate, instructed the NIH to develop a cost management plan that would attempt to avoid a fall in success rates that occurred in 1991 when the amount of money spent on each grant had increased dramatically and the length of the average grant had also increased. In 1992 we instituted a management plan that would allow for no more than inflationary increases in the size of either competing or noncompeting awards.

If we were to have reductions of the sort that are outlined in this year's budget in succeeding years out through the year 2000, we would have to reconsider whether to apply the management plan as written or whether to take reductions in the commitment base. That would, of course, affect the answer to your question quite dramatically. We have found by doing some calculations that whereas our overall success rate for grants at the moment is about 24 percent, by the year 2000 that number would be something on the order of 19 percent if we failed to readjust our management plan. If we adjusted the management plan, the reduction in the success rate would be about 2 or 3 percent.

I hasten to add that the success rate that we view as a composite for NIH is a highly variable one among Institutes and among various programs. There are segments of our portfolio in which the success rate is as low as 10 or 12 percent; the reduction in success rates for those categories would be severe if the predicted budgetary reductions were to occur.

The overall effect on our enterprise would be to slow research across the NIH, without doubt.

Mr. PORTER. I am not sure how you can say the Secretary has not specified where the cuts would come within HHS, because it is specified in the budget justification. I realize this is not binding on anyone, but it certainly has a great foreboding, it seems to me, with a billion dollars less by the year 2000 than we have today and that is in current dollars also.

Dr. VARMUS. A representative from the Department is here and perhaps might want to say a word about the Secretary's testimony in response to a similar question a few days ago.

Mr. WILLIAMS. Let me confirm what Dr. Varmus said. The illustrations in the President's budget do show NIH coming down by 9 percent. There are other accounts that are also shown in the President's budget coming down 9 percent. But if you aggregate them all, the meaning of those is that the Department itself in its discretionary programs must reduce spending by that amount by 1999. It does not mean, however, that those reductions must be applied line item by line item, but rather in the aggregate we are committed to reducing by that total amount. The Secretary will make decisions, some priority decisions on how to do that, and there are a number of things going on now, part of them in Reinventing Government, Phase II which will address those reductions.

But we do not, we must not come down uniformly by those reductions line item by line item.

REVIEW OF NIH'S PUBLIC EDUCATION AND COMMUNICATION EFFORTS

Mr. PORTER. It means to me that even without attempting to bring the budget into balance, that increasing costs of entitlements are crowding out even the highest priorities in discretionary spending. And it means to me that we had better all get honest about it and sit down and do something about entitlements or there will not be any discretionary spending left.

Let me ask now, Dr. Varmus, you and I have talked a great deal about promulgating the good news about NIH and you referred to it in your oral and your written testimony. We have talked about making this information known to the average citizen in our country so that they can understand it. I think if we can get that message out, that it will deepen the respect and support NIH has not only across the country but here in Congress as well, because we have a very responsive government.

Last year, the committee asked you to undertake a comprehensive review of your public affairs and communications effort not necessarily with an eye to expanding it but to focusing and targeting your message more effectively. I know the review is still under way but I wonder if you can tell us what you have found so far and how you plan to enhance your communications effort.

Dr. VARMUS. I would be pleased to do so.

Under the direction of Ann Thomas, our communications office has been very active in considering the request of last year's deliberations. The most visible manifestation has been to hold a forum at the NIH in the new Natcher Building about two months ago to allow communications experts from around the country to discuss with NIH communications officers the challenges that we face.

Many interesting things came up during the course of that two-day meeting.

Perhaps the most important was an effort to identify the ways in which NIH can best get information to consumers. To me, one of the most powerful messages was delivered by Kate Jamieson from the Annenberg School of Communications in Philadelphia, who pointed out that although it is useful to have reports of NIH findings in the public media, the most important thing was to teach people how to gain access to the information they need when they need it. And that can be done most effectively these days through telephone, a computer, and other means of rapid communication.

So we are placing increased emphasis—through some reinvention programs to the Library of Medicine, through the Cancer Institute, and other mechanisms that involve the communications offices—in trying to teach people how to access NIH—delivered or NIH—produced information. For example, one can call 1–800–FOR–CANCER and get information about the latest cancer therapies and trials. One can dial or call up through the Internet a wide variety of services, including clinical trials information-delivered in lay language or in language for the health care professional.

Mr. PORTER. How many times this year have you been on network or public or cable television?

Dr. VARMUS. Very few. Occasionally. We are negotiating for the development of a public television show that will be produced by the Maryland Public Television Network, and we have other projects of that kind under consideration. Of course, I depend upon invitations to appear on such shows.

Mr. PORTER. I was going to say there are probably very few means. There have not been any problems. The media only shows things that are wrong. They never tell the American people——

Dr. VARMUS. That is why I might say I am fortunate.

Mr. PORTER. They never tell the American people all the good things that are going on and the achievements being made. I wish we could change that, though. I wish that your testimony this morning could be seen by every single American. I wish they would have an opportunity to have you interviewed about the wonderful things that NIH do so that they not only would understand them but would be more supportive. They would receive, I think, a degree of inspiration about humankind in their own country and their own institutions that they very much need.

NUMBER OF TRAINED RESEARCH SCIENTISTS

Let me ask about the overproduction of scientists. Over the Christmas holidays, the Washington Post ran a series of articles on American science which asserted the nation is overproducing scientists at a rate that Federal funding cannot continue to support. The article said the number of biomedical scientists increased 47 percent from 1987 to 1992 when the work force as a whole grew only 4 percent with an annual growth rate of medical scientists of 9.4 percent, outstripping the annual real increase in NIH funding.

Do you agree with this analysis? Is part of the concern about success rates really tied to overproduction of scientists?

Dr. VARMUS. Okay. I can't vouch for the accuracy of all the numbers but the general trends described in that article I think are accurate. The issue for us is: What is NIH going to do about this? And can it do very much?

We support the development of biomedical scientists through two mechanisms, through our training programs and through the salaries of both graduate students and postdoctoral fellows who work on our research grants.

Through those mechanisms we pay for about 15 to 18 percent of those who are in training. We pay for those who are particularly outstanding, for those destined for the most successful careers. We cannot, by ourselves, determine the size of the biomedical research enterprise, and we are extremely reluctant to retreat from our determination to support the very best of the trainees in our discipline. We believe that biomedical research has a great future. There are remarkable opportunities, and we should not shrink from our responsibility to continue to train people who will be outstanding biomedical scientists.

That being said, we recognize that there is increased tension about research grants; that competition for money is severe; that there are many young people who are dispirited.

In devising our training programs, we are guided, as the Congress has instructed us to be, by biannual reports from the National Research Council of the National Academy of Sciences that analyze the status of training in biomedical research. To date, the unemployment rates have not appreciably increased. There is tension, there is anxiety, there are failures to obtain research support, but there is not gross unemployment.

Moreover, there are new options for those who receive graduate degrees in biomedically related subjects. For example, there are new opportunities in biotechnology. There are traditional opportunities in the pharmaceutical industry. More biomedical scientists are going into allied professions—in the law, in education, in journalism, in finance, all of which we think enrich the general culture.

It is not up to us to determine the absolute number of trained biologists. We are of course very interested in that, but we cannot determine that number by reducing the number of trainees we support.

Your question also addresses a much larger issue to which we are giving some very serious thought. Biomedical research has been a growth industry for nearly 50 years, and it is now turning into a steady state industry. For the last four years, our budgets have remained more or less equal to the inflationary rate, and I proposed to our staff that in the course of the next year we should carefully study how the biomedical research community and enterprise should look under steady state conditions. This is something that will involve not just the NIH but the universities and other agencies that have a role in biomedical research.

GRANT SUCCESS RATES FOR YOUNG INVESTIGATORS

Mr. PORTER. Dr. Varmus, you touched on this, but the National Research Council reported last July that the number of grant applications from young researchers fell 54 percent from 1985 to 1993. I wonder if you could tell us what are the success rates for first-time applicants, for those resubmitting unsuccessful applications for another review, and, for those grantees competing for a first-time renewal? Do you have that kind of data?

Dr. VARMUS. Well, in general, the success rate for a new application, a so-called type one as opposed to a competitive renewal, is about twofold lower. So that if the average rate is roughly 24 percent, new applications might have a success rate of about 18 percent. And the success rate for renewal applications would be about twofold higher. That number, of course, varies, again among Institutes and, it varies among programs, ranging from roughly 15 percent to as high as 30 percent for new applicants and from roughly 29 or 30 percent to even as high as 50 percent for renewals in other Institutes.

The question of why there have been fewer applications over the last few years from investigators who are under the age of 37 is a matter of intense interest to us. I have been consulting with my colleagues at the National Academy of Sciences as they try to understand the factors that are responsible for this decrease.

Clearly, a major factor is connected to increased employment opportunities in biotechnology. All of us who have run large laboratories have seen a change in the migration of our trainees into industries as opposed to traditional academic jobs. In such industrial positions, they no longer are required to apply for grants.

In addition, there has been an aging of our training population; that is, folks wait longer before they obtain an independent academic position in which they would be required to apply for grants.

Then there is a tendency for many new investigators, given the difficulty of obtaining independent research support, to become a member of a program project grant and obtain their initial support that way. In that situation they would not appear in our records as primary applicants for grants.

All these factors are clearly important and we are trying to sort out which ones are playing the largest role.

Mr. PORTER. Well, they are important, but how do you view them overall? Are they worrisome? Troublesome?

Dr. VARMUS. In some sense they are worrisome. But I think they reflect the general tendency I mentioned a moment ago; that we are approaching a steady state. We need to understand that individuals who are trained by academic laboratories and go into biotechnology positions are doing good science and serving a useful role. We need to have a clearer idea of what the industry will look like 5 or 10 years from now, and that may be difficult to project.

There is no doubt that academic positions are becoming saturated. I hear frequently about advertised academic positions that are responded to by as many as 200 or 300 or 400 applications. It is clear that there are fewer new academic investigators per year now than there were 5 or 10 years ago. That may have a great deal to do with the decrease in the number of applications we receive from first-time grant applicants.

PRIVATE SECTOR INVESTMENT IN BIOMEDICAL RESEARCH

Mr. PORTER. When we are talking about steady state, we are talking about academic research. What about business research; is that steady state also?

Dr. VARMUS. As you know, there has been increased investment in biomedical research from the private sector. It is now roughly 50 percent of all research and development in the biomedical area.

I think that is something we need to factor into our consideration of what this enterprise will look like over the next 5 or 10 years. But I think it is very important to remind this committee that the expenditures that are made by the private sector—by the biotechnology companies and pharmaceutical companies—are very tightly linked to the investment made in biomedical research by the Federal Government.

It is sometimes argued that the Federal Government can retreat from its support of biomedical research because the private sector is spending more. My view is just the opposite. The reason that the private sector is spending more is because fundamental research carried out through the NIH and other Federal agencies has provided the seed corn with which the private enterprises are sowing their programs for development.

Mr. PORTER. Ms. Pelosi.

Ms. PELOSI. Thank you very much, Mr. Chairman. Welcome Dr. Varmus.

Dr. VARMUS. Thank you.

Ms. PELOSI. As you know, Dr. Varmus, our Chairman, Mr. Porter, and Mr. Natcher were the two leading proponents in the Congress and in the country of NIH, and so to hear him say what he said about your testimony is heartening indeed. I want to associate myself with his remarks regarding your forceful justification of your budget request and very excellent testimony. It certainly gives us all hope to hear what you are doing over there.

Dr. VARMUS. Thank you.

MAJOR BREAKTHROUGHS IN HIV/AIDS RESEARCH

Ms. PELOSI. Especially hearing it come from Mr. Porter, who, as I say, is a champion as we all know on this issue.

Every chance I get as a representative of San Francisco and in the Congress, and I know I speak for others who share that representation, I want to say how proud we are of all of your work at NIH. It gives us courage that whether it is a person with AIDS or the Nobel laureates who were here last week—or was it two weeks ago now—that you are where you are, and it is clear that your work has enabled NIH to maintain and attract a most excellent professional team to do the good work that you do.

I wanted to say that I think that what you have said and what you are doing is indeed an investment in our future. As far as the Chairman's line of questioning just now, it reminds me of conversations that we had on the Intelligence Committee, which of course I cannot discuss here, about the work that we do at the Federal level and how it relates to the industrial base and, in this case, the biomedical research base in terms of professionals coming up in the field and support for their work and all of the spin-off from that. So for economic reasons as well as health reasons, we all appreciate the importance of your work and the particular perspective that you bring and the clearer understanding you have given to us of what is happening among the young researchers.

I have a couple of questions. It is my understanding that this has been an important year for progress in AIDS research, as you have testified and as the papers have reported. Besides the importance of findings leading to the prevention of HIV transmission from mother to child and the protease inhibitors which you also addressed in your remarks, what other major findings have there been?

Dr. VARMUS. There have been a number of other findings in the therapeutic domain. For example, there has been recent evidence from clinical trials that combinations of drugs are going to be effective. Those combinations will soon include some of the protease inhibitors we have discussed. It is my personal belief that over the course of the next several years we will have combinations of drugs that will allow someone with HIV infection to live a normal lifespan.

A second development that I think is extremely important received some publicity, but it may be difficult to understand. Scientists have recently shown that even in the late stages of the disease, it is possible to show that drugs that inhibit the growth of the virus can reduce the levels of the virus within two days by as much as a hundredfold. This effect is accompanied by a marked increase in the level of CD–4 positive cells. This shows that the immune system has a great deal more resilience than one might have anticipated. The results also show that the amount of virus production is truly extraordinary. At any one time most of the virus that appears in the blood is being produced by cells that were infected only in the last few days. That shows, to my mind, that the approach of trying to inhibit the growth of this virus is extremely well justified and gives increasing hope to those who are working hard to develop such drugs.

Another important development has been the solution of the detailed structure of the important enzymes of HIV: the famous enzyme reverse transcriptase, the almost as well known protease, and now the third one, known as integrase. And I would predict, given the advances made in the study of this third enzyme, that there will be drugs effective against it in the not-too-distant future as well.

Ms. PELOSI. That is great.

Dr. VARMUS. In addition, there is new understanding of patients who have been carrying the virus (HIV) for a very long time and have not gotten sick. Dr. Fauci and others have illustrated many of the properties of those individuals and give us additional ways to think about how to confer that state upon all HIV infected individuals.

One other thing: a recent clinical trial at the NIH has demonstrated the effectiveness of IL–2 in the treatment of chronically infected individuals.

Dr. Paul might wish to add a few things to the list.

Dr. PAUL. That is an excellent list. Indeed, Dr. Varmus covered all the points I would have made.

I would emphasize the potential importance of the ability to elevate the number of CD–4 cells with interleukin-2 in HIV infected individuals, as Dr. Lane has recently described. Furthermore, the clarification of viral dynamics in HIV infection will provide us with insight into the design of combination therapies. My own view is that the joint use of the effective antiretroviral drugs together with immune manipulation offers us the best prospect for a durable control of the disease and the virus in infected individuals.

CROSS-OVER BENEFITS OF AIDS RESEARCH ON OTHER DISEASE AREAS

Ms. PELOSI. Thank you, Dr. Paul.

Dr. Varmus, when the Nobel laureates were here, I was so pleased to hear Dr. Phillip Sharp's answer to a question from the panel about what we can learn from AIDS research that is useful across the board in basic biomedical research. Could you also describe any direct advances in understanding of AIDS, and what we are learning about other diseases and other challenges?

Dr. VARMUS. I'd be happy to.

One of the things unusual about HIV infection and AIDS is the large number of disciplines that are brought to bear upon the problem—virology, immunology, behavioral science, vaccine development and drug development. The materials that we have at our disposal, thanks to the long-term investment we have had as a Nation in virology and immunology in particular, have given us a tremendous opportunity to understand fundamentals in molecular and cellular biology through the study of this disease.

I would point to a number of things that have been extraordinary about this effort. First of all, as Dr. Sharp pointed out, protease inhibitors had never been used before in the treatment of viral illnesses. They have been used in the treatment of certain other diseases, like hypertension, through the inhibition of cellular proteases. But the opportunity to treat viral illnesses with novel kinds of drugs may have tremendous ramifications in the treatment of viral illness.

As you know, we have very few drugs that are effective in viral illnesses. Any viewer of Outbreak, the recent movie starring Dustin Hoffman and described in some detail in today's Health section of the Washington Post, will recognize that viral illnesses can be extremely dangerous. So drug approaches of the kind used for HIV may have tremendous benefits in considering the development of therapies for other viral illnesses.

I would point out also that the intense interest in AIDS research has generated new means of drug discovery, of drug approval, and of clinical trial mechanisms. These are going to prove extremely useful in thinking about how we approach the approval and the testing of drugs in many venues.

The availability of molecules that are important in AIDS, some of the viral enzymes and some of the immune proteins that govern the immune system—has furthered structural biology in major ways and provided the means for considering new structure-based methods for developing drugs.

Our understanding of the immune system has advanced tremendously through the study of HIV. There have been behavioral intervention programs that have been successful in trying to prevent the spread of HIV. We all understand in the context of AIDS how important it is to prevent infection. Any individual who is defended from HIV is one individual who does not get the disease, who saves the country $120,000 in treatment costs, and who is prevented from becoming a carrier who can transmit the virus to others. The extreme importance of prevention in this context has given rise to a number of strategies for trying to intervene in the transmission of the virus, while developing new methods I think will be useful in other contexts as well.

Ms. PELOSI. Thank you, Doctor.

Once again, Mr. Chairman, I wish colleagues on the other side who are new to the committee could have heard that because I think everyone should be encouraged by the progress that is being made in this research.

Mr. PORTER. I certainly agree with you on that.

Ms. PELOSI. Thank you, Mr. Chairman. I assume, Mr. Chairman, champion of the NIH, that my time has expired.

Mr. PORTER. Your time has expired.

Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman, and welcome, Dr. Varmus. As you know very well, you have many admirers and supporters of the NIH, and I too want to associate myself with our Chairman's and Representative Pelosi's remarks.

This is a time of evaluating every government service and trying to make decisions as to cost effectiveness and where to invest. Certainly, there is no better example of a wise investment than the NIH. As a Representative from New York, we understand that not only are there critical benefits to the research community and to health and to the future of this Nation, but certainly to the economy. In the New York region, whether it is New York Hospital or NYU or Columbia and on and on and on, we estimate there is probably about a billion dollars of investment to our economy. It is very, very important. So we thank you for your leadership and we are delighted that you are with us today.

INCLUSION OF WOMEN IN CLINICAL TRIALS

I would like to focus on an article that was actually in the New Republic some time ago concerning women in clinical trials. There have been recent media reports on the issue. NIH's policy on inclusion of women in such trials has been the subject of discussion, and the article states that NIH pushes inclusion of women to the detriment of science. I know that the article has the story all wrong and I think it would be very helpful for this committee if you can discuss the issue with us and set the record straight.

Dr. VARMUS. Thank you, Mrs. Lowey.

Let me say first of all that I have written a response to that article, which I hope will appear in a forthcoming issue of the New Republic, trying to set the record straight. Far from being a divisive mechanism that upsets the progress of research, we believe that inclusion of women and minorities is good science; that it is important; that, most importantly, it works.

Under the supervision of Dr. Wendy Baldwin, we have looked carefully at all the studies that are done under the rubric of these guidelines. We found extremely few cases in which investigators have had difficulty in complying with the guidelines' strictures and in those cases where there have been difficulties, it has been possible for us to assist investigators to obtain the necessary collaboration that would allow them to include adequate numbers of minorities and women to make their studies representative.

We do not want to make a mistake of failing to identify either patients who would respond or would fail to respond to drugs because we have not included them in such studies. We have very reasonable guidelines for outlining how investigators should devise the representation of patient populations. We believe that these are effective and long overdue stipulations that guide our clinical research.

Mrs. LOWEY. Thank you.

Did you want to add to that?

Dr. BALDWIN. We have been very pleased. We have been reviewing all the trials that began during a period from where the guidelines were issued but before the actual guidelines had been pushed, and we found few cases, as Dr. Varmus said. In the few cases we found, they had been easily remedied through portfolio balance or expanding the study to include a more representative population. So we have, in contrast to the article, actually experienced how the guidelines work and think they are working just fine.

WOMEN AND MINORITY REPRESENTATION IN TRIALS

Mrs. LOWEY. I think it is important to, for the record, to explain that the inclusion of women and minorities actually improves the study because what we have been concerned about is the response of women and minorities to particular treatments or medications. To have excluded them in so many of these clinical trials, it would seem to many of us, certainly did not advance science and deal with diversity in a population. I don't know if you want to comment on that.

Dr. VARMUS. I think you have said it very well. I agree with you entirely.

Mrs. LOWEY. I think it is so important because when many of us came to Congress in 1988 we were amazed and it almost became a joke and a cliche that there were many studies where women were not included at all. When we are looking at the impacts of this work on women and minorities, it just seemed amazing to us and not very good science not to include them. Thank you.

Dr. VARMUS. Dr. Baldwin wants to make a comment.

Dr. BALDWIN. The key to that is the science basis and the guidelines. We have had guidelines in place to ensure the inclusion of women and minorities in the early stages of research. In fact, what the legislation did was to say if you get to that Phase III stage, where you already know there are differences, that there is variability that needs to be taken into account in order to ensure the results of that trial will be appropriate for everyone. Then on the basis of the science, in fact, we sort of change the calculus as to what that inclusion level has to be. So the emphasis in the legislation was clear that you could not get to that Phase III clinical trial stage and not be assured the results would be appropriate for everyone.

Mrs. LOWEY. One other point in closing, because I think it is very important in the article. It actually criticized the Women's Caucus. I think it is important to note that it was scientists who brought this issue to the Women's Caucus's attention. So often in a whole range of issues in the Congress, it is not the individual group that discovered the inequity or the need for legislative remedy, but it was scientists, men and women who came to us and said: "This is an important issue, and we would appreciate it if you can carry the mantel." So I think that is important to note and I appreciate it.

NIH RESPONSE TO IOM RECOMMENDATIONS ON CLINICAL RESEARCH CAREERS

Dr. Varmus, in September of last year, the Institute of Medicine issued a compelling report on careers in clinical research. The report sounded an alarm about the loss of physicians from the ranks of our nation's researchers and highlighted particularly the difficulties physicians have training for and pursuing careers in patient-oriented research. The report offered some specific recommendations as to steps the NIH could take to enhance the environment for clinical research and clinical research training. Could you explain to us what the NIH has actually done to examine and implement the IOM recommendations?

Dr. VARMUS. Yes, thank you. We have been very concerned about that report and with the status of clinical research in general. Even before the report was official we had invited William Kelly, the chairman of the report committee, to come to NIH to discuss the problems with our Institute Directors.

I have been concerned personally with the status of clinical research in this country—with the need for oversight of a variety of problems, such as training, monitoring of clinical trials, and funding of clinical research. To try to make some progress in these areas, a number of things are being done.

First of all, I have named Dr. Lawrence Shulman, well-known to you as the previous director of NIAMS to be my emissary to visit clinical research centers around the country and to report to me on the difficulties that are being experienced by clinical investigators.

Secondly, I am in the process of putting together a commission that will represent clinical investigators from both extramural institutions and the NIH, intramural programs to advise me about how we should improve the situation for clinical investigation in this country.

Thirdly, we are putting into place a new clinical research training program at the NIH. We expect this to be a model for how clinical research training might be affected in many places around the country.

Fourthly, we have put into place a new training program, inspired by Mr. Stokes' pioneering efforts with loan repayment, to try to attract more minority physicians into clinical research. We believe there is a particular lack of minority investigators in clinical research, and we are trying to repair that by the new loan repayment program for physicians from disadvantaged backgrounds.

PEER REVIEW OF CLINICAL RESEARCH

Mrs. LOWEY. Following up on that, in reviewing the Division of Research Grants analysis of how patient-oriented research applications are reviewed, I found it alarming that the study concluded that patient-oriented research fares less well in the peer review process than laboratory research.

Could you comment on that?

Dr. VARMUS. Yes, I would like to comment on that. It turns out that it is true with certain caveats. Patient-oriented research does particularly poorly in study sections that do not review very many patient-oriented grant applications. We are making efforts, as we reevaluate the functioning of our Division of Research Grants, to try to ensure that fewer of those grant applications are reviewed by some of the less experienced study sections.

As you probably know, the director of the Division of Research Grants has announced his retirement. As a prelude to the recruitment of the new director to the Division of Research Grants, we are undertaking a fairly widespread study of how the Division operates.

Your comment also has to be interpreted in the light of the observation that clinical investigators—those who are pursuing patient-oriented research—do as well as laboratory-oriented investigators when they come in with reapplications. When their first application fails to be funded and they come back with a second application, they do as well as the other types of investigator. That suggests to us that the patient-oriented investigator may have been inadequately trained in how to write a grant application. This is symptomatic of a broader problem, I believe, in the training of clinical investigators.

Clinical investigation is not a simple matter. In fact, in many ways it is more complex than laboratory research. It involves not just the research itself but the monitoring of protocols, the establishment of specialized review panels to do the accounting work, and the oversight work that is not necessarily a part of conventional laboratory research. We need to have investigators who are more schooled than they currently are in such methods. I think that schooling should include careful instruction in how grant applications are prepared.

Mr. PORTER. Thank you, Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

Mr. PORTER. Mr. Dickey.

Mr. DICKEY. Hi, Dr. Varmus. How are you doing?

Dr. VARMUS. How are you?

NIH EFFORTS IN BEHAVIORAL RESEARCH

Mr. DICKEY. I have a question and I don't know if it is going to take a little bit to get it out. Some of us are concerned about the costs and the expenses that we have to incur in running government and running excellent programs like you have. I am looking at one instance here where we are going to an expense to protect people from, or to cure people from diseases that are caused because of their behavioral practices, such as lung cancer and AIDS.

Now, if we have other diseases that afflict people without any actions on their part at all, my question to you is, are you doing anything to try to promote behavioral changes for better health and, therefore, freeing money up to go to those diseases that are not connected to behavior? Does that make sense? Anywhere close to making sense?

Dr. VARMUS. Let me see if I can deal with the questions.

Mr. DICKEY. That is a Southern question.

Dr. VARMUS. Well, I will try to give you a Northern answer.

In cases where behavior has an impact upon the development of disease, and I would argue there is hardly a disease in which behavioral components do not apply, the NIH has three kinds of responsibilities:

First of all, we have the responsibility of trying to define how the disease arises and how a certain action, like smoking, might contribute to it.

Secondly, we have the responsibility of trying to communicate those findings to the public. We believe that a major impact is achieved by letting people know that smoking is bad for you because it produces lung cancer.

Thirdly, we have a responsibility to try to develop means to deal with a population that does not respond simply to the announcement that some behavior is noxious to health. And that is a more contentious and difficult enterprise in my view, because we do not yet have the methods available to make profound changes in certain patterns of behavior.

But I believe that behavioral scientists are making some advances in those areas. The issue is to what extent are we going to invest in efforts to see changes in behavior that will prevent disease and changes in behavior that will help to treat disease. Because one of the major problems in the behavioral component of medicine is compliance with a medical regimen we know to be effective.

Now, the NIH invests roughly $850 million a year in a variety of behavioral research, and we believe that that money is being spent for projects that could have major impacts. We are interested in trying to assess those impacts. It is not necessarily straightforward to do so. I would agree with you, if we have more success, we will bring down the costs of health.

Now, bringing down the costs of health by reducing behavior related disorders does not necessarily free up money for what you referred to as other kinds of diseases. Because I think it is very difficult to name any single disease in which there is no behavioral component.

Mr. DICKEY. What about rheumatoid arthritis?

Mr. PORTER. Mr. Dickey, if I could interrupt for just a second. I want to ask Mr. Bonilla to take the Chair. I have been called to the Rules Committee and then I have a press briefing with the Chairman of the full Committee at 11:30. Mr. Bonilla, if you would take the Chair, you may continue.

Mr. DICKEY. Mr. Bonilla will be prejudicial to my interests.

Mr. PORTER. Never.

Mr. DICKEY. He has already shown a discrimination against me. Please keep going.

Dr. VARMUS. You raised the issue of rheumatoid arthritis. Now, I am not necessarily an expert on that disease but I do know that the treatment of that disease is extremely complicated; that there are stress influences——

Mr. DICKEY. No, no. But how do you get it? There has to be some things that are less related to activities or social patterns.

Dr. VARMUS. Yes, I would agree, in that case that is right. But there are behavioral components that govern the adequate treatment of the disease and recurrences of the disease that we do not understand.

Mr. DICKEY. The problem I am having is and I have to explain it to my constituents and I am not saying there are a whole lot of them, but the ones that do come at me are at a high intellectual level and they are saying, here we are, all we are doing is spending money in areas which allow people to continue to harm themselves or continue to harm those people who they come in contact with.

The alternative is not acceptable to me and I voted that way. The alternative is not to pull the money down and say, if you all want to create harm to yourself and those people socializing with you, go ahead and do it, we will not spend any money. But by the same token, we do not want to spend money to condone those activities, do we?

Dr. VARMUS. Nor do we want to blame individuals who under the pressures of life have incurred diseases that are devastating to them and to the public.

NIH GOALS FOR THE HUMAN GENOME PROJECT

Mr. DICKEY. Well, I think you have answered it. I want to move on to something else but I am still concerned in that area.

The Human Genome Project. What are your goals? Have you already stated those? I came late. What are your goals with that project?

Dr. VARMUS. Well, there are many goals. At the moment, one of the primary goals is developing a detailed map of the human genome for the purpose of facilitating isolation of genes that are important in disease. Over the course of the next several years—by the year 2005, according to the original blueprint that was laid down some years ago—the genome project will have resulted in the complete sequencing of the human genome.

In addition, the genome project is analyzing the collections of genes, all the chromosomal information, in a number of other organisms that are important for experimental reasons. Particularly the round worm, fruit fly, yeast, bacteria, and the mouse and the rat.

The effect of all this—which is incidentally on schedule and under budget, as you will hear from Dr. Collins, the head of our Center for Human Genome Research—is quite amazing. As I mentioned in my introductory remarks, one of the most dramatic accomplishments of this year and the preceding few years has been the isolation of a number of genes that are important in cancer, in a variety of neurological diseases, and others.

Our understanding of such diseases of course is being advanced rapidly. Our ability to make early risk assessment is growing dramatically, and——

Mr. DICKEY. Let me ask you a question. Just in the coming year, the next 12 months, what do you hope this project will accomplish?

Dr. VARMUS. Well, in the next 12 months there will be a more detailed map of the human genome. There will be a number of sequencing projects that are moving at a great rate. It is hard for me to predict exactly which genes will be isolated in the next year. Groups are working very hard on a number of genes that we know through traditional genetic studies to be responsible for a wide variety of diseases. There are at least a thousand diseases that are caused by the inheritance of abnormal forms of genes, and those——

GENETIC DISCOVERIES IN HEART DISEASE

Mr. DICKEY. Let's say heart disease. Are we making any advancement in that area?

Dr. VARMUS. Absolutely.

Mr. DICKEY. Can you describe some of that?

Dr. VARMUS. One example is through the study of a protein called myosin, which is a major component of the heart muscle. Investigators at the NIH—in the Heart, Lung, and Blood Institute—have developed a deep understanding of a disease that frequently affects the hearts of young athletes, and the affected gene has now been isolated and mutations analyzed.

Mr. DICKEY. How about old athletes?

Dr. VARMUS. Pardon?

Mr. DICKEY. Does anybody care about old athletes? Please go ahead. Excuse me.

Dr. VARMUS. Well, I can give you an example there. We know that among the proteins in our body that are responsible for heart disease, one of them, an important one, is the receptor for certain lipoproteins that are involved in cholesterol metabolism. At least in some segment of the population, mutant forms of such receptor proteins are important in the development of cardiovascular disease.

CLINICAL APPLICATIONS OF GENETIC RESEARCH

Mr. DICKEY. I try to get these things down to where it has a practical result. But if we get that gene isolated and we see what is happening, is that the sort of thing that can be handled with a nutritional program? Are we going to end up saying this gene needs to be, what?

Dr. VARMUS. I would not want to prejudge the consequence of understanding a disease before we understand it, but one solution might be nutritional. It might be the development of drugs that would interfere with the development of the disease. It might be a recommendation to change certain components of life-style.

Dr. Collins reminds me of something that appeared in many of the newspapers over the last week. Genes have been isolated by Utah investigators, that account for the so-called prolonged Q–T syndrome that is responsible for abnormal heart rhythms and premature death.

These genes affect the channels through which small molecules, called ions, travel in the heart muscle. I think it is premature at this stage to say exactly how we would translate the identification of those genes into specific therapies, but it is not difficult to imagine the kinds of therapeutic approaches that might be taken now that we know the genes that are responsible for these disorders.

Mr. DICKEY. I have one more question. I know I am out of time. If you can isolate the gene that causes you to fall asleep at 2:00 or 3:00 o'clock in the afternoon, I would appreciate that. Can you help me with that?

Dr. VARMUS. Dr. Collins can do just about anything. We will take care of that.

NIH SUPPORT FOR RESEARCH IN DIABETES, HEART DISEASE AND STROKE

Mr. BONILLA [presiding]. I would like to second that. If we did not have to sleep, we could all be more productive.

Dr. Varmus, it is good to see you here again and so many of our researchers here. We need a bigger room when you show up. It has been a pleasure getting to work with you all and to know you all in the last couple of years. The tour that you gave us in January was very helpful and we learned a lot, even though we were only there for a short period of time.

I think it is significant, in spite of what happens in elections, that there continues to be bipartisan support on this committee for the work you are doing, and even with the dispute over funding for the AIDS programs—it was restored after initially being rescinded—I think demonstrates there is a concern on this committee to continue helping you with your good work.

One of the things I would like to start with involves a lot of figures and perhaps you heard about the discussion that this committee had last week regarding numbers in terms of people affected by AIDS. I want you to understand that my line of questioning is not because I am opposed to funding for AIDS or any particular area. I wish we could give as much money as you needed for every area of research that we could, but I want to make sure this committee is getting accurate information and I want to make sure that as we have to make tougher decisions as money becomes tighter that we make them in the best interest of the entire population.

For the past week we have been struggling with these numbers. I have an article that was written by Secretary Shalala from yesterday's Washington Times and I am sure that you or your staff have reviewed it. In the article she said the toll that AIDS takes on our country is sometimes swallowed up in a sea of stats. I will read from here because there are a lot of numbers I will throw at you in the next minute or so.

In 1994, an average of 220 Americans were diagnosed with AIDS every day. That is one person every six minutes. And in 1994, an average of 109 Americans died of AIDS every day or one person every 13 minutes. The number of AIDS-related deaths is growing at an annual rate of 24 percent and more Americans died of AIDS in 1994 than were killed by handguns. That is something that the Secretary wrote, those were her remarks from the article.

I want to point out for the record that over 1,700 people each day are diagnosed with diabetes. That is one every minute. Seven million people are not even diagnosed. Four hundred thirty-eight people die each year from diabetes, which is one every four minutes—four times the rate of AIDS. Each year, 160,000 people die from diabetes, four times the number killed by handguns. One hundred sixty thousand is roughly the size of Little Rock, Arkansas or Laredo, Texas.

I also want to point out for the record that heart attack, stroke, and other cardiovascular diseases remain America's number one killer and it has been the case since 1919. Each year, more than 925,000 Americans died from heart attack, stroke, and other cardiovascular diseases. Specifically, 480,170 Americans die each year from heart attack; 143,640 Americans died each year from stroke. Currently, about one in four Americans, or 58.9 million Americans, suffers from heart attacks, strokes, and/or other forms of cardiovascular disease. More than 2,500 Americans die every day from heart attacks, stroke, or other cardiovascular diseases or one person every 34 seconds. Specifically, more than 1,300 Americans die every day from heart attack, or one person every minute from heart attack. More than 390 Americans die every day from stroke, or one person dies every three and one-and-a-half minutes from stroke.

Last time I checked in this country, we had a pretty good handle on how to avoid AIDS. So with that in mind, what message is Dr. Varmus and this Administration sending about the importance of diabetes, cardiovascular and stroke research?

Dr. VARMUS. Well, as you know, Mr. Bonilla, we do have major investments in all of those areas. Those investments are increasing.

We have done very important work in diabetes over the last several years, such as the Diabetes Control and Complications studies. A number of studies in your own area that have been supported by the NIDDK and the Office of Research on Minority Health have been trying to increase our ability to control, understand, and treat diabetes. Similar things can be said about heart disease.

I am very cautious, however, about attempting to link the amount of money we spend on any disease to the frequency of disease in any rigid fashion. We have to allocate our money for research in accord with a number of other factors, including the scientific opportunities and the human resources to pursue those avenues of investigation. To assess these, we also consult with our colleagues in the extramural community about where they think the opportunities lie. We have to consider not simply the effect of any research projects on the disease that seems to be immediately addressed but also implications for other diseases, as I was explaining to Ms. Pelosi.

I believe that we have made such resource assignments in that way and that it has been very effective. I have no axe to grind with respect to the numbers that you have laid out. We know the cardiovascular disease is more common than AIDS. Tremendous progress has been made in the reduction of mortality due to cardiovascular disease and stroke—over 50 percent reduction in mortality from heart disease and over 60 percent reduction in mortality from stroke—as a result of our investment in these areas. We believe things are going well.

Our judgment is that we cannot appropriate simply in accord with the numbers of people who are affected. But it also has to be said that HIV is a major health problem in this country. It is the leading cause of death in individuals between the ages of 25 and 44. It is, overall, the eighth most common cause of death. There are 40,000 deaths per year, roughly the same number as can be attributed to breast cancer. It is also a disease that is caused by an infectious agent with tremendous research opportunities, as you have heard, for understanding a variety of other diseases.

JUSTIFICATION OF FUNDING FOR AIDS RESEARCH

Mr. BONILLA. I voted to restore funding again, as I mentioned in my opening remarks, for the AIDS research.

Dr. VARMUS. For the Ryan White Program.

Mr. BONILLA. That is right. That was initially rescinded understanding of course that we need to continue the support of research. There is, however, a lightning rod effect that is associated with AIDS, right or wrong. It is positive and negative, depending on who you talk to. In fact, I hear a lot of concern expressed to me from good researchers that are working primarily in the area of cardiovascular disease and cancer.

Why do you think that it is such a lightning rod and seems to stir up as much controversy in the research community as it does in laymen's circles?

Dr. VARMUS. Well, as you know, the spread of HIV is connected with controversial behaviors, and it also represents an enormous threat. It is unusual for us to be confronted with a virus which, if acquired is likely to be a death sentence. These are dramatic events.

Epidemics like this occasion dramatic discussion. Fifteen years ago, the disease and the virus were unknown; now 40,000 people die each year of the disease, many are infected each year, and as many as 100,000 new cases of AIDS are diagnosed in a year. This is going to induce tremendous discussion.

We believe that HIV/AIDS is a potentially controllable illness. It is one that we would like to have a vaccine against but we do not. The prospects for obliterating this infectious disease seemed very great to the population that grew up in an era in which it was thought we were going to eradicate all infectious diseases. Vaccines gave the public tremendous hope that biomedical science could eradicate infection. We now know, through the appearance of AIDS, the reemergence of tuberculosis, and the attention being given to the Hantaan virus and to a number of other exotic viral agents that infectious diseases are very much with us.

AIDS has stirred tremendous interest because it is caused by an outside force that invades human beings and is transmitted from one person to the next. I think it is understandable that this kind of plague will attract tremendous public attention.

FUNDING FOR AIDS RESEARCH

Mr. BONILLA. Doctor, do you hear the concern expressed from researchers in areas of heart disease and cancer as well? Have you heard these concerns expressed to you as well about what they perceive to be an unfairness in terms of research dollars allotted?

Dr. VARMUS. I would not say unfairness. Everyone in biomedical research is concerned about the difficulty of obtaining grant support. The difficulty of obtaining a grant in the AIDS area, however, is no different from the difficulty in other areas. The success rates are very, very similar. Individuals working on HIV as well as those who are studying heart disease and cancer are concerned about the availability of research support.

I think particularly in the area of cancer research one finds very little of the kinds of complaints you are mentioning, because those who study cancer recognize the tremendous synergism between AIDS research and cancer research. For example, we were able to identify the AIDS virus rapidly and develop a blood test that protected recipients of blood transfusions because of past investments in retroviruses through the study of cancer.

Similarly, patients with AIDS develop cancers of various kinds and the investment we are making in the understanding of a full panoply of AIDS-related diseases includes studies of a variety of cancers—lymphomas and Kaposi's sarcoma. Just recently the study of Kaposi's sarcoma has resulted in the isolation of a new herpes virus that has implications that are much broader than simply AIDS.

Mr. BONILLA. Dr. Varmus, for the record, if you would, I would request that you provide me with the cost per death of the following diseases: HIV/AIDS, diabetes, cancer, heart disease and stroke. I would appreciate.

Dr. VARMUS. Cost per death or the amount we spend on these diseases per death?

Mr. BONILLA. Correct.

[The information follows:]

RESEARCH SPENDING PER DEATH FOR SELECTED DISEASES

The HHS research funding per death for HIV/AIDS, diabetes, cancer, heart disease, and stroke is based on the National Center for Health Statistics Provisional Vital Statistics Data as of October 1994. Comparison of these diseases, however, is not directly comparable since HIV/AIDS is a contagious disease, whereas diabetes, cancer, heart disease, and stroke are chronic diseases.

	FY 1994 research spending ($000)	Number deaths	Funding per death
HIV/AIDS	$1,508,138	38,500	$39,172
Diabetes	300,303	55,110	5,449
Cancer[1]	2,004,583	530,870	3,776
Heart disease	781,447	739,860	1,056
Stroke	114,571	149,740	765

[1] Excludes NCI HIV/AIDS cancer funding.

Source: Office of the Assistant Secretary for Health.

Mr. BONILLA. I have one more question in a different area before we move to a second round. What was your reaction, Dr. Varmus, to a recent Louis Harris poll that states the good news is that Americans highly value medical research more than any other type of research? The bad news is that medical research is connected with some institutions that are not thought of favorably at the moment; namely, the Federal Government, the pharmaceutical industry, and hospitals.

Dr. VARMUS. Well, I am pleased they applaud the research enterprise. But I think we have to do some work to convince them that the Federal Government is good for you. I like big government.

Mr. BONILLA. Dr. Varmus, thank you.

At this time, I will move to Mr. Riggs. Are you prepared at this time?

Mr. DICKEY. Prepared for what?

Mr. BONILLA. Because if you would like, I can move to Ms. Pelosi and come back to you. It is up to you.

Mr. RIGGS. Mr. Chairman, please ignore the comments of my colleague here from Arkansas. I don't want anybody here to think we are possibly discussing UCLA and Arkansas in the NCAA Championship, because this testimony is too important.

Mr. BONILLA. At this time I will yield to Ms. Pelosi, and then we will come back to Mr. Riggs.

ROLE AND ACCOMPLISHMENTS OF OFFICE OF AIDS RESEARCH

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. Chairman, I want to point out, following up on your and Mr. Dickey's question, that the importance of the AIDS research is a little different in that this research is for a cure and a vaccine. In much of the research that is done we are trying to find a cure.

But before Mr. Dickey walks out of the room, I want to point out that in many of the illnesses for which we are trying to find hope, behavior plays a role—not just AIDS, but in many others. Of course, there is a genetic predisposition to some other illnesses, be it heart disease, et cetera. Nonetheless, behavior and diet and stress also play a role. So it is not just the case with AIDS. In fact, a lifetime of overindulgence and you have heart disease to deal with or maybe it is not over a lifetime but a long period. For some young people one mistake and you have a terrible sentence. I hope it is not a death sentence.

Dr. Varmus, could you describe the coordinating and planning role of the Office of AIDS Research in your office, and what progress has been made in the last year in OAR's planning efforts? Briefly, because I have a few more questions.

Dr. VARMUS. Well, briefly, then. When Bill Paul graciously agreed to take on this job, he was confronted with putting together a coordinated plan for the 1996 budget within a matter of six weeks. He did this expeditiously. We have a coordinated plan that, as you know, addresses five major areas—behavior, epidemiology, pathogenesis, treatment, and vaccines—and he has consulted with all the Institute and Center directors to develop a budget that meets the ambitions of each of the Institutes. As you know, AIDS is a very complex subject, it involves all of our Institutes and Centers. And developing this coordinated budget has been a major task.

In addition to developing a coordinated budget plan and research plan, he has been involved in developing a review strategy so that we can evaluate over the course of the next year what the AIDS program in NIH has achieved over the last decade. He has obtained the services of a large number of very admirable investigators, headed by Arnold Levine, the chairman of biology at Princeton, to carry out this effort to help us plan the future of AIDS research.

Ms. PELOSI. So you view it as a positive aspect of——

Dr. VARMUS. Absolutely. It has been tremendously successful, in my view.

ADMINISTRATION OF THE AIDS RESEARCH PROGRAM

Ms. PELOSI. Some have been critical of OAR's consolidated line-item budget authority. What is your view? Do the planning budget process and budget authority add to the bureaucracy or eliminate redundancy by allowing better coordination and planning?

Dr. VARMUS. I will answer that in a couple of ways. Dr. Paul's office has been tremendously efficient in developing its budget plan using no more than roughly 30 FTEs. They have efficiently received and distributed the money that is involved in this effort.

I understand the concerns of Institute directors who feel that having the money go to a centralized office takes away some of their authority and budget planning responsibilities. No one likes to lose money from their budget line. Some of our Institute directors—Dr. Fauci is good example—are extremely good planners and very knowledgeable about AIDS; it could be perceived that the revised method for distributing money is an incursion on his responsibilities.

What I would like to see—and what I believe has occurred to a very significant extent—is strong collaboration between the Institute directors, particularly those who are deeply engaged with AIDS, and Dr. Paul's office to develop a budget, one that is responsive to research needs and coordinated with Institute programs. We have many opportunities for overlap and for collaboration, so we need to try to take advantage of Dr. Paul's office to be sure that we spend our money as wisely as possible, especially in this difficult period.

BREAST CANCER RESEARCH

Ms. PELOSI. Thank you, Dr. Varmus.

On another subject, it is my understanding that the Administration is requesting $426 million for research on breast cancer, an increase of $49 million, or 13 percent.

How does this level of funding relate to the Secretary's national action plan on breast cancer and what will this level of funding allow NIH to do in terms of basic research and prevention and treatment of breast cancer?

Dr. VARMUS. As you know, tremendous advances are being made in breast cancer research, especially over the last couple of years. This was illustrated this year by the isolation of the gene BRCA–1 that contributes to one hereditary form of breast cancer that accounts for about 5 percent of cases. But in addition, tremendous strides have been made in understanding other genes that are involved in the nonhereditary forms of breast cancer. There have been advances in treatment through the use of Taxol. In addition, we are engaged in a clinical trial for prevention with the use of Tamoxifen.

A specific answer to your question with regard to the Secretary's breast cancer action plan is that roughly $10 million of the FY 1995 budgetary request will go to the action plan, and that amount will be increased by $10 million in FY 1996. The action plan is being developed through Susan Blumenthal's Office of Women's Health in the Department. It involves not simply the NIH but also the CDC and other agencies, and we are working closely with Dr. Lee's office and the other agencies in developing that plan. Many NIH employees, including Ed Sondik, the Acting Director of the NCI, are on the planning committee, and we expect to have a cooperative and productive process.

ENVIRONMENTAL CAUSES OF BREAST CANCER

Ms. PELOSI. You have answered my next question which was going to be about the Office of Research on Women's Health. So I am going to just ask you a question that I asked Dr. Bishop.

You are aware, I am sure, that several years ago Congresswoman Lowey's district was determined to be the area of highest incidence of breast cancer. Now, unfortunately, our area, the Bay Area, has ranked number one in that regard. Number one, number two, number three, whatever it is. It is across the country. As you know, breast cancer affects every family in America.

I was asking Dr. Bishop about what the possibilities were for more research about the environment, since an isolated area seems to have more cases than another area, and his response, I think, if I understood correctly, was that whether it is the environment or whatever we find out about in the laboratory, then that is where we should be focusing. And when I said environment, I did not necessarily mean the food we eat, I meant sort of the air we breathe, although I know our diet is environmental as well.

Can you address what prospects there might be for looking for environmental causes of breast cancer?

Dr. VARMUS. I will try to explain Dr. Bishop's answer because I think it was a very cogent answer to your question. We know from either comparisons of rates in different parts of the world or indeed in different parts of this country that there must be environmental components instrumental in causing breast cancer. The differences that occur among your district, Mrs. Lowey's district, and many others are very small.

Ms. PELOSI. Small, yes.

Dr. VARMUS. And that accounts for the difficulty in doing an epidemiological study that is revealing about specific environmental factors.

Ms. PELOSI. Excuse me one second. I think in Mr. Bonilla's area as well there is a high incidence.

Dr. VARMUS. Breast cancer rates are high in many parts of the country. The highest incidence level differs by a very small increment from many others. That is what makes identification of environmental factors difficult. It is simpler to do an analysis that reveals environmental sources of disease when there is a tremendous difference between one area and another. Subtle differences are very difficult to analyze. That has a major role in our difficulty in specifying environmental hazards that are instrumental in the causation of breast cancer.

Dr. Bishop was suggesting that we make use of the way in which environmental factors are believed to have an impact upon breast cancer—through the causation of mutations. We know about at least 10 genes that are subject to alterations at the DNA sequence level as a consequence of exposure to a variety of environmental insults. What he was arguing is that our best approach to identifying the environmental agents that are responsible for breast cancer may be to look directly at the genes and the mutations rather than to attempt a difficult epidemiological analysis.

He described some examples that have been very useful in the context of other kinds of cancers. For example, mutations in melanomas are sometimes identified as mutations induced by sunlight because they have certain chemical characteristics of mutations caused by ultraviolet light.

We know that mutations induced by a carcinogen called aflatoxin, an inducer of hepatic cancers, also have certain molecular signatures that allow us to say that liver cancers are caused by that environmental agent. We hope that by a molecular analysis of the genetic damage in breast cancer we may actually learn the answer to the question of what environmental agents may be most important. This might be more effective than the much more difficult epidemiology toxicology, and other traditional means of approach that have, frankly, not yielded very much substantial information about breast cancer over the course of many years.

Ms. PELOSI. And is there heavy focus on this?

Dr. VARMUS. Yes, there is. In fact, one of the initiatives under the list of NIH initiatives in the 1996 budget request is for the study of genetic damage and environmental insult.

Ms. PELOSI. Well, I think that in closing, Mr. Chairman, I believe that on two of the issues we have talked about today, AIDS and breast cancer, our country is well served by your being where you are. Certainly that was clear from your testimony and your responses on AIDS, and of course the international recognition that you have received on the issue of cancer and what the payoff will be for women and all people in the families of America as we do this research on breast cancer. So I thank you for your testimony. More importantly, I thank you for your leadership and all that you bring to the job you have before you, including this excellent team that you have here today.

Dr. VARMUS. Thank you very much.

Ms. PELOSI. Thank you, Mr. Chairman.

Mr. BONILLA. Thank you, Ms. Pelosi. Mr. Riggs.

Mr. RIGGS. Thank you, Mr. Chairman, and good morning again to the witnesses. I do apologize for coming in late for what is a very, very important hearing for this subcommittee. I had a conflict with another Appropriations subcommittee down the hall and was called away because of the flood situation in California. So my apologies. In fact, I did not go with FEMA and Leon Panetta to California today so I feel somewhat guilty I am here and they are——

Dr. VARMUS. As a homeowner in California, I am grateful to you for your efforts.

COORDINATION OF AIDS RESEARCH

Mr. RIGGS. More importantly, I might alert my colleagues on the subcommittee that as we approach what is sure to be a rather contentious debate on the House Floor over the supplemental appropriations and rescission packages, that I am aware of two bipartisan amendments that would further cut funding for FEMA in order to restore certain housing programs under the jurisdiction of the VA, HUD and Independent Agencies Subcommittee. My concern is, with the latest round of flooding, obviously, we are probably going to need to increase the amount of disaster assistance funding going into California rather than decrease that. But that is somewhat of a side issue to the hearing this morning.

I do want to point out a process related issue, and I think Mr. Bonilla will support me. It is quite likely, as Chairman Porter indicated, we may be able to have further focused hearings of the subcommittee in May as we approach the process of marking up a budget resolution and then get to the task of writing the fiscal year 1996 appropriation bills. As one member of the subcommittee, I can alert you in advance that I will have further, very specific questions about NIH. We may want to discuss them either privately or before this subcommittee during that month of May before undertaking those budget deliberations in what is obviously going to be a very competitive, even austere, budget climate.

Having said that, let me turn to some specific issues and concerns. One is my perception, and I may be wrong on this—if I am I would certainly appreciate it if you could set me straight—that within NIH we have taken a somewhat fragmented approach to dealing with the national crisis of AIDS and the spread of HIV-related diseases in America. Your budget request reflects funding that is spread out over a number of the Institutes, and I am wondering whether the time has come when we ought to look at some consolidation so that we can really bring a focus and the resources to bear on solving the spread of this deadly disease?

Dr. VARMUS. In my view, Mr. Riggs, that is exactly what we have done through the creation of the Office of AIDS Research. Because AIDS is such a complicated disease—involving research concerned with therapies, vaccines, viruses, the immune system, behavioral components and others—every Institute has had something to bring to this fight. Recognition of that complexity could lead to three outcomes. One would be chaos; one would be the creation of a new institute, which I think none of us is particularly interested in making; and the third is to develop a coordinated effort through an office that oversees the budget and program development in collaboration with Institute Directors and other informed individuals.

Dr. Paul heads such an effort. I believe it is highly coordinated. Through the NIH, Revitalization Act of 1993, he has been given added responsibilities and authorities that have allowed him to command the respect and talents of many outside NIH, as well as inside NIH, to help in deliberating about how best to spend our money to wage this war.

BUDGET INCREASES IN AIDS RESEARCH AT NIH

Mr. RIGGS. I would ask Dr. Paul, your budget request for fiscal year 1996 represents, if I understand it, a 3 percent increase over fiscal year 1994 appropriation levels.

Dr. PAUL. I believe the budget request for fiscal year 1996 represents an approximately 5.4 percent increase over the previous year.

Dr. VARMUS. He asked about 1995.

Dr. PAUL. I am sorry. Are we asking 1996?

Mr. RIGGS. I want to know the incremental increase from 1994 to 1995 and 1995 to 1996.

Dr. PAUL. Three percent from 1994 to 1995, which was given to us based on the committee's deliberations. The initial request, I believe, was 5.9 percent or 6 percent.

NIH STREAMLINING EFFORTS

Mr. RIGGS. Let me also ask, because I am interested in the general area of consolidation and streamlining wherever prudent. In your budget justification you talk about some of the changes that you have implemented within NIH pursuant to the Government Performance Review Act and about a streamlining process. Are you at a point where you have been able to actually identify and quantify a cost savings that has resulted from these consolidations and streamlining efforts?

Dr. VARMUS. I would find it hard to give you a precise number, but we certainly have been saving FTEs. We have been decreasing the costs for some of our review processes. I will give you one example. Through the work of Dr. Wendy Baldwin, Deputy Director for Extramural Research, we have been able to allow grant applicants to delay the submission of many forms that are required for applicants. Since only 25 percent of our applicants are successful, this means that 75 percent never need to submit such forms. That saves literally hundreds of millions of dollars in institutions around the country and at NIH through a simple maneuver, that is, in a sense a streamlining actually occurs within the context of a reinvention laboratory that our extramural program enjoys.

We have been very forceful in trying to develop such things and we are looking for FTE reductions through other mechanisms at NIH. For example, by developing service centers that would allow Institutes to use a centralized facility for a variety of administrative services, by developing a more efficient, computerized administrative system, that would allow us to decrease the number of people who are involved in our administrative procedures; and by new means of running the intramural program. Computerized procurement operations, for example, are going to save tremendous amounts of time, money, and personnel in obtaining materials for research.

Mr. RIGGS. Help me out with something. As a layperson, you talk about increases to high priority research areas. Obviously, you are dealing with matters that involve life and death. I am wondering, how do you internally, how do you prioritize where our funding should be?

Dr. VARMUS. These are complicated matters. What we do is try to identify areas where research is proceeding well and where the need is great. Through discussions with Institute Directors and discussions that frequently involve outside consultants, we try to decide where the emphasis is going to be.

Now, I should say two things about this. The planning goes on not only NIH-wide, but also within each Institute. Each Institute has a certain amount of liberty to decide how it is going to allocate its funds.

We also are very clear about the historical importance of investigator-initiated grants. It is a basic tenet of my administration, and I believe the administration of most of the Institute and Center Directors, that overdetermination of where the money is going to be spent is a mistake; that top-down direction is going to close off the opportunities simply by preventing many imaginative investigators from getting the chance to show what they can do with their own imagination and their own drive.

BUDGET PRIORITIES AND INCREASES IN AIDS INCIDENCE RATES

Mr. RIGGS. Are you aware of the considerable discussion that we had in this subcommittee about the documented increase in the number of reported AIDS cases?

Dr. VARMUS. Yes, I am.

Mr. RIGGS. What bearing does that have on your budget request? And is there some question or doubts about those statistics?

Dr. VARMUS. There is only uncertainty as reflected in the discussion here about the interpretation.

Let me just emphasize once again something that I think David Satcher from the CDC was able to clarify for you last week. The analysis is complicated because the definition of AIDS was changed, starting in 1993, so that patients who have a reduction in CD–4 levels below 200 per ml are now designated as having AIDS, but they would not have been so designated in previous years. That meant that a number of individuals who in 1991 and 1992 were not considered to have AIDS were designated at the start of 1993 as being AIDS cases. The result is the number of AIDS cases shot up at the start of 1993 by capturing a number of people not so designated in 1992. The inevitable consequence of that was in 1994 the numbers of cases was lower because so many cases from previous years had been captured in 1993.

Mr. RIGGS. So your budget request has been responding to the statistics?

Dr. VARMUS. No, I will come to that with my next point. My answer thus far was an effort to clarify the confusion about the incidence of the disease.

The next point, our budget request is not linked directly to the numbers. It is linked to the massive problem presented by the AIDS conundrum to our country. The bottom line here is that we have 40,000 deaths a year from this dreadful disease. It is an infectious disease, it affects young individuals, and we msut do everything we can to combat it. Our budget determination is based on the scientific opportunities and the general importance of the disease, but it is not going to be affected by simple numerology.

Mr. RIGGS. Mr. Chairman, are you going to entertain another round of questioning? If so, I will withhold. I have a couple of other questions I would like to pose at the appropriate point.

Mr. BONILLA. Why don't I come back to you after I yield to Mrs. Lowey. I have a couple of questions as well so we will get them in, Mr. Riggs.

Mr. RIGGS. Thank you.

Mr. BONILLA. I yield to Mrs. Lowey at this time.

THE WOMEN'S HEALTH INITIATIVE

Mrs. LOWEY. Thank you, Mr. Chairman, and I want to thank you for the important work you are doing on women's health initiatives in addition to the areas we were talking about before.

I have read the letter from Jerry Klepner from HHS concerning the PEPI study. In many meetings in my area, and around the country, women are continually questioning whether they should take estrogen replacement therapy. Maybe it is just a question in my age bracket, but this is of great concern to us. I look forward to the additional information that will come out of this study. I hope we do not have to wait nine years.

But before I ask you a question about that, because I would like you to give us some information, I would just like to comment on my colleague from California, Mr. Riggs', statement previously, which gives me cause for great concern.

We all share the concern for California and the damages brought by natural occurrences and disasters, whether it is floods or earthquakes, and we certainly want to assist in any way we can. But I am very concerned that my colleague mentioned that they might come back for additional funds for FEMA. And, in fact, I am not aware that the Governor of California has canceled his commitment on a $7 billion tax cut for the people of California.

So my colleague from California is supporting cuts in a whole range of programs in this committee. I am aware of increasing numbers of disasters, but I am also aware of an increase in AIDS, breast cancer, and a range of illnesses, increases that may come as a result of our cutting back on prevention programs and education, which I think are as important as investments in research. So I would just say that I hope my colleague is not going to come back and ask for additional cuts in this committee as a result of needs for FEMA.

And, again, I want to mention we share the concerns of the people of California, but I think maybe they should consider the $7 billion tax cut and use that to pay for their own disasters, with all due respect.

In any event, with regard to the Women's Health Initiative, we spoke last year about the NIH's work on the Women's Health Initiative and the necessity of continuing the historic work about expanding our understanding of women's health issues.

I mentioned the letter which we received concerning the change in using estrogen and progestin and I wonder if you could bring us up to speed on the implementation of the Women's Health Initiative, where will the initiative go this year? Is there any information that is available or just in general can you give us an update on where it is?

Dr. VARMUS. Yes, let me place the PEPI studies you are referring to in context with the Women's Health Initiative. The PEPI study, as you know, was funded by the National Heart, Blood, and Lung Institute and addressed the effects of replacement hormones in post menopausal women on some indicators of cardiovascular disease—namely, blood lipids. The study provided very promising results: "good" cholesterol was increased and "bad" cholesterol was decreased with replacement therapy.

The PEPI study also sounded a note of caution that you alluded to. It is important to oppose estrogen with progesterone to decrease the risk of endometrial cancer. This is being done in the Women's Health Initiative, which is being run by the Office of Prevention in the Office of the Director.

Mrs. LOWEY. The information I got is that the Women's Health Initiative has responded to the PEPI study.

Dr. VARMUS. It is definitely coordinated. I am just clarifying for you where the administrative structure resides. The Women's Health Initiative (WHI) is designed to measure not only in changes in lipids but, more importantly, the outcomes of those changes. So it is a much longer-term study and a much more expensive study.

I will bring you up to date on the WHI. As you know from our discussion last year, the coordinating center was established in Seattle in September 1992. Sixteen vanguard clinics were named in March of 1993, and 24 additional centers were established in September of 1994. Participants have been enrolled since September of 1993. Over 8,000 individuals have been brought into the study and provided with their initial evaluation and assignments to various treatment groups.

The planning and the focus of community prevention will be finalized during 1996. As Dr. Kirschstein reminds me to tell you, the enrollment in the study is ahead of schedule. That is important because the study, as you know, is intended to extend as long as the year 2006, and it is important to keep this kind of thing on track.

As you recall, last year we discussed our response to a study by the Institute of Medicine that had evaluated the Women's Health Initiative. The IOM was concerned about the costs. I am pleased to say that we have been able to keep within the costs that were originally projected by the planners of the initiative.

Mrs. LOWEY. Okay. Well, thank you very much. The time is late and I just want to tell you that so many of us are supportive of this initiative and that I look forward to the continuing progress reports. We thank you for your important leadership.

Yes, Doctor?

Dr. KIRSCHSTEIN. Mrs. Lowey, we might tell you that when we testify on behalf of the Office of Director activities, Dr. Bill Harlan, who runs that study, will be here and will be pleased to add information for you.

Mrs. LOWEY. Well, thank you very much. We appreciate that.

STRATEGIES FOR SETTING FY 1996 RESEARCH PRIORITIES

Mr. BONILLA. Thank you, Mrs. Lowey. I have a couple of questions, Dr. Varmus, and if Mr. Riggs returns we will return to him.

How did the NIH set its greatest potential research priorities for this year? Did you use any statistical data such as years lost of potential earnings in particular areas or cost per death? Let me clarify, because I know it was perhaps not an understanding about cost per death. What I mean by that is the amount of research dollars spent in relation to the number of deaths that occur in this country. So were those factors included in your priorities for greatest potential research?

Dr. VARMUS. No, they were not.

Mr. BONILLA. What factors do you use in considering what your areas will be concentrating on?

Dr. VARMUS. The areas we have advertised as special areas of emphasis for this year are going to receive, as a result of our initiatives, a very small fraction of our total budget. They are meant to indicate to the Congress what will be done with at least some fraction of the extra money we are asking for.

The major consideration was the degree to which we could further important areas of developing research through some additional increase in expenditures. In some cases those increases were designated because we felt there was a specific technology-based concern. For example, we know that the genome project can proceed more rapidly if we develop sequencing technologies based on miniaturization procedures and other technological developments that can be furthered by a fairly small investment. In addition, we all recognize, including Members of this committee, that we have been undersupplying the extramural research community with money for shared instrumentation. That is why we asked for additional funding to try to restore the shared instrumentation program to something that approaches its previous level of support.

In a broader arena, we felt that progress had been made in neurobiology, cell biology, and genetics, and that such progress would foster our understanding of connective tissue diseases, brain diseases, and other diseases for which there might be preventive strategies developed. We wanted to make special use of those opportunities by trying to obtain additional money to support them. But we did not carry out the kinds of actuarial analysis you are suggesting.

DISEASE AFFECTING OLDER CITIZENS

Mr. BONILLA. I would like to ask you about a theory that some say that research for diseases and medical problems that affect people over the age of 65, some feel that is not a wise decision. I, frankly, think it is insulting to a lot of elderly members of society because oftentimes in this day and age they are, for example, the parents and they contribute so much to society, and with our longer life spans, even for a greater period of time. CDC takes this into account, and I am delighted they do not write off people over the age of 65. But what do you think of ideas that say that more attention should be paid to people under the age of 65 and less to the elderly?

Dr. VARMUS. Well, Mr. Bonilla, I think your question feeds our own source of pride at what NIH has accomplished for the country. Sixty-five is no longer old. One of the reasons it is no longer old is because we have had tremendous gains in our ability to improve the Nation's health through research that has been sponsored by the NIH. So, we agree entirely, and we have deep concern with the disorders of the elderly.

We also have to recognize that because of the success of NIH-sponsored research and the general improvements in the economic well-being of the country, the demographics of the country are changing very rapidly. I suspect you will hear from Dr. Hodes, the head of the Aging Institute when he makes a presentation to you, that the ranks of the elderly are growing at a tremendous pace. Some of the diseases that are very frequent among those in their seventies and eighties, including cardiovascular disease, stroke, Alzheimer's disease, and others, need to be dealt with. Simply postponing the onset of Alzheimer's disease by 10 years would save the country a tremendous amount of money and would afford tremendous relief from personal hardship and suffering. For all of these reasons, we have a very deep commitment to the diseases of the elderly.

I should also point out that benefits to the elderly are not simply tied to what is labeled "aging research." Many of the things we are learning about fundamental biology—the behavior of blood vessels or the behavior of nerve cells—irrespective of an immediate connection to aging will be beneficial as we try to understand those diseases that occur frequently in the elder age groups.

Mr. BONILLA. Very good. At this time, Mr. Riggs, I will yield to you for additional questions. My understanding is that Ms. Pelosi has additional questions as well; is that correct?

Ms. PELOSI. Mr. Chairman, I can submit mine for the record if we are waiting for Mr. Porter. I would go ahead and ask them, but in the interest of the committee's time, particularly the Director's time, I don't have to ask these questions unless we need the time.

Mr. BONILLA. We will conclude with Mr. Riggs and, Mr. Riggs, at your conclusion if you will recess the committee until 2 o'clock. Unfortunately, I have to run to another meeting myself. So Dr. Varmus, thank you for being here. It is good to see you all.

RESEARCH PROGRESS IN ALZHEIMER'S DISEASE

Mr. RIGGS [presiding]. I will be happy to do that and I will be brief because I know we probably all have lunch time commitments.

I came at the very tail end of your response to Mr. Bonilla's question regarding elderly diseases. One of the things I wanted to ask was, particularly since President Reagan's illness the public has obviously focused attention on the problem of Alzheimer's Disease. What is happening in that area? Are we making any progress in the research and treatment?

Dr. VARMUS. I will address that briefly. You will hear more about this from the testimony from the Directors of the Neurology and the Aging Institutes. There are a number of things that have happened in the last year that are of special moment.

First, a mouse model for Alzheimer's disease that was recently announced offers a tremendous opportunity for trying to understand how the disease arises provides a system in which new therapeutics can be attempted.

Second, as we described here last year, Alzheimer's disease has been linked to a specific genetic locus that encodes the Apo E–4 protein, offers new insight into pathogenesis. There have been new tests proposed for early diagnosis. There have been developments of behavioral strategies that assist in maintaining as high a cognition level as possible in patients with this disorder. There is a new drug called Tacrin, which has had some effect in improving memory and other cognitive functions in patients who are undergoing the ravages of Alzheimer's disease.

So there has been progress. We are particularly encouraged by our deeper understanding of neurobiology and the exact nature of the neurofibular tangles and amyloid plaques characteristic of this disease.

INVESTMENT IN ALZHEIMER'S DISEASE

Mr. RIGGS. I was not able to find the specific line-item details so could you briefly summarize for me what we are talking about in terms of a dollar commitment?

Dr. VARMUS. It is currently $311 million, most of which is being spent by the Aging Institute, but there is also a commitment to Alzheimer's disease at other Institutes, especially the National Institutes of Neurological Disorders and Stroke.

Mr. RIGGS. Are you making an increased budget request this year?

Dr. VARMUS. We have, yes.

Mr. RIGGS. How much in this particular year?

Dr. VARMUS. Two-and-a-half percent this year, but there was a dramatic increase in spending during the course of the 1980s in response to a congressional mandate.

NIH SUPPORT FOR RESEARCH AT ACADEMIC INSTITUTIONS

Mr. RIGGS. Yes.

Now let me ask another question. You talk about in your testimony supporting health-promoting research at nearly 2,000 of our countries' colleges, universities, and other scientific institutions. How much of your total budget is in fact devoted to research at academic institutions or through academic institutions?

Dr. VARMUS. It is approximately 50 percent.

Mr. RIGGS. About 50 percent.

Dr. VARMUS. Is that number—are you including independent research institutions?

Mr. RIGGS. Yes, I would, but I am excluding commercial for-profit.

Dr. VARMUS. So probably about—we will give you those numbers for the record, but it is roughly 75 percent because I don't know exactly what component goes to small businesses, for example.

Mr. RIGGS. That would be fine.

[The information follows:]

The table below displays the amounts awarded to Colleges and Universities.

SUPPORT FOR COLLEGES AND UNIVERSITIES

[Dollars in thousands]

	1994 Actual	1995 Estimate	1996 Estimate
Budget authority	$6,155,083	$6,355,047	$6,599,214

INVESTMENT IN PRIVATE SECTOR COLLABORATION

Mr. RIGGS. In the area of collaborations with private industry and promoting research by commercial ventures, how much of your budget is devoted to that?

Dr. VARMUS. Again, that analysis would be tricky. For example, in academic institutions there is a substantial amount of research that now goes on through sponsored research agreements in which a laboratory may receive some money from industry and some money from the Federal Government.

At NIH itself, we have a few hundred investigators who are working under so-called "CRADA" agreements to pursue research with industrial support. So I think I would want to give you an accurate number, and I would have to do that for the record.

[The information follows:]

In FY 1995, the NIH is supporting 151 full-time equivalents (FTEs) with non-appropriated funds.

CONTRACTS WITH COMMERCIAL INSTITUTIONS

Mr. RIGGS. Are there arrangements whereby academic institutions sometimes contract or subcontract, as the case may be, with commercial for-profit entities?

Dr. VARMUS. They would not subcontract with Federal money. We do have, of course, research and development contracts directly from NIH with a number of firms.

THE EFFECTS OF NIH SPONSORED RESEARCH ON CORPORATE INVESTMENT

Mr. RIGGS. I would be interested in getting that latter figure, and also interested very quickly—this is a question I have been asking of key Administration figures as they appear before our various Appropriations Subcommittees to testify on the fiscal year 1996 budget request. When Secretary Reich talks about corporate welfare, I think he does so in a very—or he uses that term in a very broad sense. That is, in effect, I think a broad brush that perhaps may paint or touch on many aspects of the Federal budget.

Do you see yourself being involved in promoting, through your research partnerships, corporate welfare?

Dr. VARMUS. We do and we do it in various ways. Perhaps the most important single way, and the way in which we spend most of our money, is by developing new knowledge that pharmaceutical and biotechnology companies use in designing their own research strategies for the development of products that improve health.

We also do it through a collaboration with industry and sometimes through research in which we are working side by side doing similar things and communicating as any two sets of scientists would on matters of scientific interest.

Mr. RIGGS. I wish there was a way that somehow—and I don't believe it is possible for any Administration to speak with one voice—you could reconcile your comments, which are very reasonable, and even in my view very wise and progressive, with some of the rhetoric that we hear coming out of the Administration at certain times, particularly on the subject about corporate welfare. Because again, I think when figures such as Secretary Reich, given his high profile position within an Administration, talk about corporate welfare, there is a potential for backlash that might embarrass the Administration because what I am hearing is a very conflicting signal. There is a contradiction again between his use of that term "corporate welfare" in a very broad sense and some of the very pragmatic budget proposals contained in the requests of the various departments and agencies under review by us that would further promote scientific research and other forms of research on a collaborative public-private basis.

So perhaps you could convey that message or at least consider it. Because, again, I hear a contradictory and somewhat dichotomous message.

Dr. VARMUS. If that is heard by others in the Administration I think I will hear about it, too.

Mr. RIGGS. Very good. All right. I believe at this point in time the subcommittee will stand in recess and we will reconvene at 2:00 p.m. this afternoon.

Thank you to the witnesses.

[The following questions were submitted to be answered for the record:]

ISSUES RELATED TO THE RO-1 APPLICATION

Mr. Porter: What percentage of new RO-1 applications are resubmissions?

Dr. Varmus: In FY 1994, 29 percent of new R01 applications were resubmissions. This resubmission rate has been consistent for the five year period from FY 1990 - FY 1994. Currently, there is no limit to the number of times an unsuccessful application can be resubmitted in an amended version. However, the NIH through its Extramural Reinvention Committee is reviewing a proposal to limit the number of amended versions permitted to two resubmissions of the same project. That Committee is also reviewing the ways in which time-consuming resubmissions of promising applications might be avoided, for example, by increasing the use of deferrals and having Study Sections and/or Program staff request additional information which can be presented to Councils.

Mr. Porter: How many RO-1s receive "no-cost" extensions?

Dr. Varmus: In FY's 1993 and 1994 there were 364 and 339 such extensions respectively.

SUCCESS RATE FOR INVESTIGATOR-INITIATED RESEARCH

Mr. Porter: What is the success rate of grant applications submitted in response to RFAs versus investigator-initiated research?

Dr. Varmus: The success rate for unsolicited new single-investigator research project grants (RPGs) is 22 percent compared to a success rate of 19 percent for RFAs. The overall success rate for competing RPGs is 23 percent.

TOP LEVEL VACANCIES AT NIH

Mr. Porter: How many Institute directorships, deputy directorships, and scientific directorships are currently unfilled?

Dr. Varmus: There are four vacant Institute directorships: National Cancer Institute (NCI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of General Medical Science (NIGMS), and National Institute of Mental Health (NIMH). Five Institute deputy directorships are unfilled: NCI, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Enviromental Health Science (NIEHS), and NIMH. Searches are underway to fill these positions in NINDS and NIEHS. Eight scientific directorships are currently unfilled: Division of Cancer Etiology/NCI, Division of Cancer Treatment/NCI (effective April 1), NINDS, National Institute of Allergy and Infectious Dieseases (NIAID), NIEHS, National Institute on Aging (NIA), National Institute of Drug Abuse (NIDA), and NIMH. National searches are being conducted to fill all but the two NCI positions. A decision about these two positions will be made once the report of the external advisory group reviewing the NCI intramural programs has been completed.

RESEARCH SUPPORT THROUGH CRADAS

Mr. Porter: How much funding does the intramural program receive from Cooperative Research and Development Agreement (CRADAs)?

Dr. Varmus: The intramural program at NIH received $9.277 million in funding from Cooperative Research and Development

Agreement (CRADA) collaborators during FY 1993, and $7.339 million in funding from CRADA partners in FY 1994.

Mr. Porter: How much of that goes to NIH versus individual investigators?

Dr. Varmus: Virtually all of this money goes directly to the laboratory of the NIH Principal Investigators who are engaged in the CRADA research, where it is used to help fund work on the CRADA.

OUTSIDE FUNDING FOR THE INTRAMURAL PROGRAM

Mr. Porter: What are the rules regarding the receipt of outside income for intramural researchers, from CRADAs and other sources?

Dr. Varmus: All NIH employees are subject to the Governmentwide standards of conduct issued by the Office of Government Ethics. These regulations, which are supplemented by rules of the Department of Health and Human Services and the NIH, govern the ability of employees to engage in outside work activities. Because a CRADA is an official relationship between an NIH Institute or Center and an outside organization, no employee is permitted to receive income from work he or she performs as a research partner on a CRADA.

Intramural researchers at the NIH may engage in compensated consulting activities for outside organizations, if there is no conflict of interest between the scientist's laboratory or branch and the outside firm. Because of a recent Supreme Court decision, intramural researchers can also receive honoraria for speeches or written articles, if the focus of the speech or article is not work-related, i.e., a matter on which the scientist has not worked in the preceding year. Before a researcher can engage in any outside work, with or without compensation, the request is reviewed by the Institute's Deputy Ethics Counselor (DEC), who often is the Institute director. These DECs receive annual training on ethics rules, and are advised by the DHHS Office of the Special Counsel for Ethics, which maintains a staff office at the NIH.

SENIOR BIOMEDICAL RESEARCH SERVICE

Mr. Porter: We understand that you have received approval to begin the Senior Biomedical Research Service. How many slots will you use in 1995 and 1996, and how are they allocated by Institute?

Dr. Varmus: The Department of Health and Human Services has received approval from the Office of Management and Budget to begin the Senior Biomedical Research Service (SBRS). The statute provides for a total of 500 SBRS slots available to the Public Health Service (PHS). NIH expects to receive approximately 75 percent of these slots. Currently, the Assistant Secretary for Health plans to distribute 100 slots initially, and we expect to receive about 75 of these. The NIH will use these slots primarily to recruit outstanding research scientists from outside the Agency and then will use the remainder to retain and/or promote the most outstanding scientists currently in our intramural programs. NIH currently has eight intramural scientific directorships vacant; we expect the SBRS to aid us substantially in recruiting for these positions.

Because the SBRS is based solely on the scientific credentials of its members, the NIH is not allocating, on a permanent basis, a specific number of slots to each Institute. Slots will be allocated on the basis of individuals appointed to the SBRS, and will revert to a central pool when a particular person leaves the Agency or is no longer appointed to the SBRS.

SPECIAL PAY AUTHORITIES FOR PHYSICIANS

Mr. Porter: How do you anticipate using the Title 38 Authority you have now received?

Dr. Varmus: The NIH is in the process of implementing Title 38 special pay authorities for physicians. For the present, we will use this authority only for physicians who have clinical responsibilities, who actually see patients on a regular basis or provide services incident to patient care, such as diagnostic radiology. Physicians whose primary responsibility is laboratory research, and who do not see patients regularly, or those managing portfolios of grants, and who do not see patients, are not eligible. The nomination of physicians and the specific pay levels will be reviewed and approved centrally to ensure appropriate use of Title 38.

Mr. Porter: What specialties would be eligible to receive the enhanced compensation levels?

Dr. Varmus: All specialties are eligible to receive at least some of the enhanced compensation under Title 38. These include special pay for full time service, length of service, and board certification. Some but not all physicians who are covered will also receive additional compensation because they perform duties in scarce medical specialties. These rates, which are similar to those paid by the Department of Veterans Affairs, are in four ranges: $0 to $15,000, for primary care and physical medicine and rehabilitation; $0 to $20,000 for gastroenterology, psychiatry, and pathology; $0 to $30,000 for cardiology, general surgery, nuclear medicine, otolaryngology, and urology; and $0 to $40,000 for anesthesiology, cardiac surgery (open heart), gynecology, neurosurgery, ophthalmology, orthopedic surgery, plastic surgery, radiology, thoracic surgery, and vascular surgery.

Mr. Porter: Provide a chart showing the distribution of full-time permanent positions by grade level throughout the NIH.

Dr. Varmus: Total NIH employment by grade level as of September 1994 is shown on the table below:

National Institutes of Health

Detail of End-Of-Year Employment

	FY 1994
Executive Level IV	1
Senior Exeuctive Service	218
GS/GM-15	891
GS/GM-14	1,332
GS/GM-13	1,267
GS-12	1,615
GS-11	1,488
GS-10	468
GS-9	1,007
GS-8	580
GS-7	1,592
GS-6	828
GS-5	553
GS-4	207
GS-3	41
GS-2	19
GS-1	1
Subtotal	11,892
Commissioned Corps:	
CC-1	3
CC-2	24
CC-3	85
CC-4	232
CC-5	232
CC-6	369
CC-7	5
CC-8	7
Subtotal	957
Wage Grade (all levels)	1,010
Ungraded	2,065
TOTAL	16,143

FUNDING FOR INSTRUMENTATION AND EQUIPMENT

Mr. Porter: How much funding is provided for instrumentation and equipment through the direct costs of research project grants?

Dr. Varmus: NIH awarded approximately $129M in the support of scientific instrumentation and equipment in FY 1994 as direct costs on grants.

FUNDING FACILITY CONSTRUCTION AND RENOVATION

Mr. Porter: How much facility construction and renovation is funded through indirect costs?

Dr. Varmus: None. Although indirect costs are being described in terms of facilities costs and administrative costs, facilities costs, which include depreciation and use allowances, interest on debt associated with certain buildings, equipment and capital improvements, operations and maintenance expenses and library expenses, do not fund new construction and renovation. A portion of facilities costs are paid to reimburse the recipient organization for expenses already incurred for facility costs. These costs are paid as a depreciation or use allowance based on standard accounting practices for the use of the physical plant and equipment that is devoted to the conduct of research.

However, OMB Circular A-21 does require that institutions' payments for depreciation or use allowance made under sponsored research agreements be expanded to acquire or improve research facilities within five years. The weighted average for depreciation and use allowance is approximately 8 percentage points of the overall weighted average rate of approximately 51 percentage points. The amount of indirect costs paid as depreciation and use allowance for both space and equipment in FY 1994 was approximately $186M.

FINANCIAL MANAGEMENT PLAN REVISION

Mr. Porter: Last year you testified that a revised financial management plan would be complete by late summer of 1994. Has the report been completed? If so, please forward it to the Committee.

Dr. Varmus: A revised financial management plan has been prepared by the NIH Cost Management Committee. It is currently undergoing various levels of review by several policy making bodies within the agency prior to submission to the NIH Director. It is anticipated that this plan will be ready for submission to the House Appropriations Committee sometime this summer.

FTE REDUCTIONS

Mr. Porter: Identify your FTE ceilings from 1993 to 2000.

Dr. Varmus: NIH employment targets are as follows:

National Institutes of Health
Summary of FTE Ceilings

	FTE Target
FY 1993	17,129
FY 1994	16,805
FY 1995	16,197
FY 1996	16,135
FY 1997	15,817
FY 1998	15,373
FY 1999	14,903
FY 2000	14,903

Mr. Porter: What guiding principles are you using as you manage these reductions?

Dr. Varmus: A task group was charged to propose ways that NIH can meet its targeted reductions while accomplishing its mission of conducting and supporting biomedical research. The reductions include not only total FTE numbers, but also cuts in senior positions (GS-14 and above) and in all supervisory positions. The NIH is implementing a set of recommendations to help it meet this downsizing by focusing on actions that will better utilize the NIH workforce. Many recommendations will address the reengineering of work techniques, often through the use of new computerized tools.

NIH has also begun the implementation of recommendations from the final report from a distinguished advisory committee that reviewed the intramural research program. These recommendations include the consolidation of some programs to save administrative expenses and shifting some resources to more promising areas of research.

In all of these deliberations, the NIH will approach decision-making with a keen awareness of the potential impact these changes can have. Our goal in all cases is to minimize disruption to our programs and to our employees. For example, if we are able to simplify certain administrative programs as a result of de-layering or delegation to line managers, we may need to re-train employees to perform other important tasks, and re-direct their efforts to these areas.

CRADA APPROVAL PROCESS

Mr. Porter: We have heard that it takes nearly a year for a Cooperative Research and Development Agreement (CRADA) application to be approved. What steps are you taking to speed up this process?

Dr. Varmus: NIH is aware that the time period between the completion of negotiation of the research plan and other Cooperative Research and Development Agreement (CRADA) provisions and the approval of the CRADA has frequently been too long. NIH convened a PHS-wide workgroup to provide recommendations to streamline the CRADA process. Those recommendations are being incorporated into a policy and procedures manual on CRADAs which is expected to be submitted to the NIH Technology Transfer Advisory Committee for approval in April. In addition, several revisions to the process have already been made which are speeding up approval time. Approval time, as measured by the time elapsing from the date of the scientist's signature--signifying completion of the negotiation--to the date of the signature of the NIH Deputy Director for Intramural Research--signifying final approval--averaged 3.67 months for the nine CRADAs signed by both NIH and the industry collaborator so far this fiscal year. The shortest time was four days, while the longest was five months and two days.

The Subcommittee should be aware that "approval time" often encompasses time elapsed while comments and suggestions from the central NIH CRADA review committee are taken back to the company for further negotiation. This time period is thus dependent not only on the speed of the administrative process, but also the complexity of the particular CRADA and the responsiveness of the company collaborator.

Finally, the idea that a CRADA is an application that must be approved, with long delays resulting only from administrative lag, is somewhat misleading. The CRADA is scientist-driven and most often begins with NIH and industry scientists discussing their ideas for collaboration. A suitable plan for the research, description of the staffing and resource allocations, and modifications to the model CRADA provisions are then negotiated. These negotiations are not unnecessarily prolonged, but depend greatly on the complexity of the CRADA and the number of parties involved. When negotiations are completed, "approval time" begins and it is this time period that NIH has targeted for streamlining.

SHANNON AWARDS

Mr. Porter: Will Shannon Awards be funded in 1995 and 1996, and from what source?

Dr. Varmus: Yes, approximately 100 Shannon awards will be funded in 1995. They will be funded jointly by $5 million from the NIH Director's Discretionary Fund and $5 million from participating Institutes and Centers, each contributing 50 percent of the overall cost of an individual award of $100,000 for up to two years.

As the Shannon program is reconsidered anew each year, it is unknown at this point what level the program will be funded in 1996.

FUNDING FOR BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

Mr. Porter: How much funding did NIH allocate to behavioral and social science research in 1994?

Dr. Varmus: During Fiscal Year 1994, the NIH spent $776 million in research associated with health and behavior.

DIRECTOR'S DISCRETIONARY FUND

Mr. Porter: Has any funding in the Director's Discretionary Fund been obligated in 1995? How much of this funding was spent in 1994 and for what purpose?

Dr. Varmus: Of the approximately $7.5 million available in the Director's Discretionary Fund in FY 1995, $5 million has been reserved but not yet obligated for the James A. Shannon Award Program. An additional $300,000 has been reserved but not obligated for initiatives of the new Director of the National Institute on Nursing Research.

In FY 1994, the Director's Discretionary Fund was spent as follows: $4.1 million to support 101 James A. Shannon Awards; $1.9 million to support research grants in nine Institutes in the area of Decade of the Brain research; $124 thousand to support a research grant for studies of the breast cancer gene; and $134 thousand to support several other small projects, including establishment of a Loan Repayment Program for Clinical Researchers from Disadvantaged Backgrounds. A total of $6.3 million in the Director's Discretionary Fund was expended in FY 1994.

TAPS AND ASSESSMENTS

Mr. Porter: Identify the one percent set-aside tap by Institute for 1995 and 1996. Also, identify all the various taps on the NIH budget in 1995 and 1996.

Dr. Varmus: The first table displays the statutorily required one percent set-aside for program evaluation. The second table shows the taps and assessments.

National Institutes of Health
FY 1995 and FY 1996 Program Evaluation
(dollars in thousands)

ICD	FY 95 Estimate	FY 96 Estimate
NCI	$10,806	$11,119
NHLBI	6,650	6,843
NIDR	882	908
NIDDK	3,736	3,844
NINDS	3,292	3,387
NIAID	5,540	5,701
NIGMS	4,580	4,713
NICHD	2,892	2,976
NEI	1,519	1,563
NIEHS	1,380	1,420
NIA	2,197	2,261
NIAMS	1,170	1,204
NIDCD	851	876
NIMH	3,202	3,295
NIDA	2,215	2,279
NIAAA	966	994
NINR	267	275
NCRR	1,717	1,767
NCHGR	774	796
FIC	113	116
NLM	651	670
TOTAL	$55,400	$57,007

FY 1996 Estimate assumes cap on Agency for Health Care Policy Research share of one-percent evaluation assessment.

National Institutes of Health
Taps and Assessments
(dollars in thousands)

Program Evaluation:	FY 1995	FY 1996
Office of the Assistant Secretary for Health	$ 6,809	$ 7,006
Agency for Health Care Policy & Research	13,082	13,461
Natl Center for Health Statistics	19,918	20,496
Asst Secy for Planning and Evaluation	11,081	11,402
Sub-total	$50,890	$52,365
DHHS Special Projects	1,076	1,107
PHS Special Projects	5,215	5,366
TOTAL	$57,181	$58,838

EXTRAMURAL FUNDING FOR CLINICAL RESEARCH

Mr. Porter: What percentage of NIH extramural research is allocated to clinical, patient-oriented research?

Dr. Varmus: In FY 1994 NIH allocated approximately 82 percent or $8.9 billion of its funds to extramural research. Of that amount, NIH spent approximately 33 percent or $2.9 billion on clinical research involving human subjects.

FUNDING NEEDED FOR 30% SUCCESS RATE

Mr. Porter: What additional funding would be required beyond the President's 1996 request to: (1) ensure that the average success rate for NIH as a whole is 30%; and (2) ensure that the success rate for each Institute and Center is at least 30%.

Dr. Varmus: The attached table displays by Institute and Center the additional funding required to achieve a 30 percent success rate.

Three Institutes and Centers (ICs), the National Institute on Dental Research, the National Institute of General Medical Sciences, and the National Eye Institute have achieved success rates of at least 30 percent within the FY 1996 Estimate. For the balance of ICs and NIH in total, to reach a success rate of 30 percent would require an additional $515.9 million over the FY 1996 Estimate for a total of $2.0 billion for new and competing grants.

NATIONAL INSTITUTES OF HEALTH

FY 1996 Estimate				Funding Above FY 1996 Estimate To Achieve A 30% Success Rate	
Institute	Number	Amount	Rate	Success Number	Success Amount
NCI	885	$248,547	21%	404	$113,405
NHLBI	546	163,789	19%	321	96,384
NIDR	153	22,286	31%	0	0
NIDDK	407	92,071	18%	261	59,134
NINDS	450	109,694	24%	110	26,838
NIAID	638	199,584	28%	57	17,675
NIGMS	840	180,235	35%	0	0
NICHD	286	64,380	17%	211	47,385
NEI	207	45,128	30%	0	0
NIEHS	121	27,461	22%	42	9,441
NIA	268	73,360	28%	16	4,489
NIAMS	184	41,758	21%	80	18,224
NIDCD	145	29,188	25%	29	5,898
NIMH	354	79,528	18%	227	50,884
NIDA	228	60,703	21%	93	24,760
NIAAA	131	27,827	18%	87	18,565
NINR	52	12,101	12%	74	17,221
NCRR	48	8,255	26%	8	1,290
NCHGR	45	19,929	25%	9	3,986
FIC	58	1,355	24%	14	327
TOTAL NIH	6,046	$1,507,179	23%	2,043	$515,906

ADMINISTRATION OF AIDS FUNDING

Mr. Porter: Dr. Paul, we have been impressed with the way you have managed the Office of AIDS Research over the past year. The planning process you have developed and the coordinated approach to budgeting are welcome. The issue I want to raise with you today is the presentation of the AIDS budget in the appropriations bill. As you know, I have had concerns from the start about a separate line item appropriation for AIDS. Last year's bill did provide a separate line item, but also identified AIDS funding for each Institute and required you to submit a reprogramming if you proposed to transfer any AIDS funding between Institutes. In reality, your ability to allocate AIDS funding really exists more when the budget is initially submitted than after the appropriation is passed. If the Committee were to go back to the traditional process of appropriating AIDS funding within the individual Institutes consistent with your request and gave you transfer authority subject to reprogramming, wouldn't you have as much authority as you do now?

Dr. Paul: While I would certainly agree that the budget development process is critical to the authority of OAR, last year's appropriations process is the perfect example of the importance of the single line item appropriation. As you point out, the budget request last year displayed the single appropriation, but also identified proposed AIDS funding for each Institute. However, the Appropriations Committees of both Houses provided less than the President's request for AIDS research. With the new authority, OAR redistributed the appropriated funds, according to the scientific opportunities and priorities that had been identified through the planning and budget development process. Particularly when fewer funds than planned are available, this authority allows for better management of the scientific opportunities and assurance that funds will be used most effectively to address the scientific priorities. As you recall, the OAR provided this new proposed distribution to the Committee for consideration just prior to the Conference Committee on the Appropriations bill. We believe that this process worked well, more expeditiously than a request for reprogramming, and thus enabled us to execute the budget within the time constraints prescribed by the authorization.

GRANT FUNDING

Mr. Porter: Last year, you presented the Committee with an intriguing initial analysis which indicated that, over a three-year period, 90 percent of those with grants scored in the top 50 percent ultimately received NIH funding. The Committee encouraged you to continue to pursue this issue. Do you have additional information you can share with us?

Dr. Varmus: We have indeed been considering approaches to collecting additional information on investigators who were initially unsuccessful in applying for NIH grants. In addition to those who eventually obtained NIH support, we must determine what other sources of funding, if any, were secured by the the remaining investigators. We believe that a significant number of these scientists may be supported by NIH grants on which they are not the named principal investigator. We also feel that private foundations and industry may constitute alternative sources of support for those who were not awarded NIH grants.

To collect this type of data, it is likely that we will require a survey. At this time we are studying the feasibility of consolidating this data gathering effort with a customer survey that is also under consideration.

AVERAGE LENGTH OF FUNDING RESEARCH PROJECTS

Mr. Porter: Can you tell us how long on average an individual researcher receives funding for a particular research proposal, through the initial grant and subsequent competing renewals?

Dr. Varmus: The median length of uninterrupted funding for a particular NIH research grant has decreased steadily over the last 30 years. In 1965, 50 percent of first-time grant recipients received continuous funding for at least 5 years. By 1985, 50 percent received continuous funding only for at least 3.8 years. By the end of 6.3 years 75% no longer receive support for the initial project.

IMPLEMENTATION RECOMMENDATIONS FROM INTRAMURAL REVIEW

Mr. Porter: Last year a distinguished outside panel made extensive recommendations on improving the NIH intramural research program. How is NIH responding to its major recommendations? For example, has greater independence been established in the performance review of scientific directors and the tenure process? Have the Institutes established prospective planning processes to allocate resources between their intramural and extramural programs, which then feed into a campus-wide allocation?

Dr. Varmus: The report of the External Advisory Committee (EAC) on the intramural research program was transmitted to the Director, NIH, on April 11, 1994. An "Implementation Plan and Progress Report" giving detailed responses to each of the 42 recommendations made in the Report of the EAC was submitted and discussed by the Director's Advisory Committee (DAC) on December 2, 1994. The DAC unanimously approved that implementation plan, and it is currently being printed together with the EAC Report.

Major recommendations of the EAC Report related to acquisition of tenure, review of tenured scientists and Scientific Directors, postdoctoral training, organizational issues affecting recruitment and retention, NIH-private sector collaborations, allocation of funds between intramural and extramural programs, and renewal of the Clinical Center. Most of the changes suggested in the EAC Report have already been addressed by the NIH Director and the Deputy Director for Intramural Research in conjunction with Institute and Scientific Directors, and other changes are in progress.

A new tenure-track and tenure program has been implemented. This involves the use of national advertisements and search committees for entry into tenure-track, along with the requirement that tenure be recommended by a new Central Tenure Committee composed of active senior NIH scientists. Further, the selection and appointment process for members of Boards of Scientific Counselors has been strengthened, with increased oversight by the Institute Directors and the Office of the Director, NIH. Also, the review processes for intramural scientists, as well as for the individual Scientific Directors, have been tightened. Guidance on these aspects has been provided in the form of a recently revised NIH Manual Chapter 3005, "Review and Evaluation of Intramural Programs," and revised Orientation Guidelines for members of Boards of Scientific Counselors (BSCs) and ad hoc consultants. These have been discussed with the chairs of the BSCs in two meetings with the NIH Director and the Deputy Director for Intramural Research. Using these new guidelines, greater independence and uniformity of reviews has already been achieved. Independent review of Scientific Directors is being conducted every four to six years by an ad hoc committee which reports to the National Advisory Council of each Institute Center Division.

The EAC recommended prospective planning processes to allocate resources between the intramural and extramural programs. The Director, NIH, has requested that each ICD provide him with a description of such a process. The written descriptions of the processes utilized by the Institutes to make such budget allocations will be reviewed and guided by the Director, NIH, who ultimately is responsible for the overall balance between intramural and extramural funding at the NIH.

Mr. Porter: We know you have begun a review of the Cancer Institute's intramural program. Do you have similar reviews planned for other Institutes? Do you expect more uniformity among Institute intramural programs in the future?

Dr. Varmus: Similar reviews of other Institutes or Centers (ICs) are being considered based on discussions regarding the need for such an evaluation by the IC Director and the Director, NIH. The purpose of these reviews is to provide guidance on the utilization of intramural resources and on the organization of intramural programs. The particular organizational components selected for such reviews will depend on several factors, such as particular reorganization opportunities or the need to provide new leadership for a particular component.

It is expected that there will be more uniformity among Institute intramural program in the review processes for appointment to postdoctoral fellowships, appointments to tenure-track and tenured positions, and the scientific review processes for investigators, laboratories and branches, and Scientific Directors. Thus, rigorous standards for quality control will be maintained with oversight by the Deputy Director for Intramural Research and the Director, NIH. It is not anticipated, however, that central NIH will impose rigid organizational patterns or management styles upon the individual Scientific Directors in carrying out their missions. Diversity in administrative and organizational aspects may confer certain advantages in the leadership of particular intramural programs.

PANEL RECOMMENDATIONS FOR HUMAN EMBRYO RESEARCH

Mr. Porter: Dr. Varmus, I feel I have to bring up a sensitive subject because I suspect it will come up at some point this year and I want to give you an opportunity to present your views to the Committee. Last year, you appointed an outside committee to advise you on the use of the human embryos in research. That panel presented its recommendations to your advisory council last December. While the council was meeting, President Clinton issued an executive order prohibiting certain kinds of embryo research from being conducted, which contradicted some of the panel's findings. Have you made a decision about the other recommendations of the panel, which were not affected by the President's executive order? If not, when should we expect a decision?

Dr. Varmus: I am currently reviewing the recommendations of the Panel that relate to the research not affected by the President's directive and will reach a decision in the near future as to how I think we should proceed. I can say, at this point, that I firmly agree with the Panel and the Advisory Committee to the Director that an ad hoc advisory group should be formed to monitor ethical and scientific issues associated with this research on a continuing basis, to promote public understanding of the research, and to review all research proposals involving human in vitro fertilization before funding is finally permitted.

REASONABLE PRICING CLAUSE

Mr. Porter: One of the reasons cited for continuing to invest in NIH research is the development of strong basic science that is then parlayed into commercial products through biotechnology and pharmaceutical companies. But we hear many complaints from the outside community about their attempts to transfer this technology from NIH through cooperative research and development agreements (CRADAs). The major complaint seems to be the "reasonable pricing" clause, which other Federal agencies apparently do not have. We understand that a review of this clause is underway. Can you tell us where this stands, and your views about striking a balance between consumer protection and commercial development?

Dr. Varmus: At NIH, the principal mechanism for transferring technology from our research laboratories to biotechnology and pharmaceutical companies is the licensing of government owned intellectual property arising from research which did not involve CRADAs. During the period of fiscal year 1985 through 1994, NIH executed 598 licenses, only 16 of which resulted from CRADAs. Thus, during this period CRADA licenses represented 2.67 percent of our total licenses to industry.

During the same 10 years, NIH generated a total of $76 million in royalties, consistently leading all other federal agencies combined in generating royalties. During fiscal year 1994, NIH generated $18.6 million in royalties--about two-thirds of all FY 94 federal government royalties, according to the Department of Commerce. Out of this very impressive royalty stream, only $4,500 came from products we licensed as a direct result of CRADAs. That is 0.02 percent of our total royalties, and represents a tiny fraction of NIH technology transfer activities.

Despite this unparalleled success by NIH in the federal technology transfer arena, NIH is aware of the reported frustrations of companies trying to transfer NIH technology through the CRADA process. NIH has been concerned about the possibility that the so-called "reasonable pricing" clause has inhibited the ability of our scientists to interact cooperatively and productively with their private sector counterparts.

To review the current policy and obtain advice and recommendations on the advisability of removing or modifying the clause, NIH convened two public meetings in July and September of last year, inviting representatives from Congressional offices, the scientific community, industry, academia, and the public. One view that emerged from both was that the clause should not be allowed to impair NIH's ability to engage in collaborative research to improve public health. Another view was expressed that NIH should not become involved in the pricing decisions of its commercial partners, because it lacked expertise in this area and such a role conflicts with its statutory technology transfer mission.

NIH also obtained similar advice from other external and internal groups, including the Director's Advisory Committee, the PHS Technology Transfer Policy Board, and the NIH Technology Transfer Advisory Committee. Currently, the Department is reviewing options regarding modification or removal of the clause and NIH expects a resolution of the issue very shortly.

UNDERWRITING INTRAMURAL RESEARCH FUNDING

Mr. Porter: Do you foresee a time when CRADAs could be used to underwrite a substantial portion of the NIH intramural program?

Dr. Varmus: No. The number of co-funded CRADA projects is minuscule compared to the number of basic research projects undertaken by NIH scientists, and the resultant distribution of funding reflects this. FY 1994 funding from NIH CRADA collaborators was $7 million, about one-half of one percent of the total intramural research budget of $1.201 billion for that year. At any given time, the 100 or so ongoing CRADA projects are far outweighed by the over 2,000 intramural research projects ongoing within the intramural research program.

In addition, it is unlikely that co-funding through CRADAs would ever be possible or desirable for the substantial support of the basic biomedical research conducted at NIH. CRADAs appropriately involve the transfer of future intellectual property rights to the collaborator for the commercialization of the results of the research. Collaborators are generally interested in collaborating on "applied" type research projects, which build on the more fundamental research conducted by NIH scientists. These "applied" projects are more likely to generate results which can be commercialized. Thus, the primary mission of NIH, strong basic science, could not be accomplished through CRADAs.

RECOMMENDED FUNDING LEVELS FOR RPGS

Mr. Porter: For the record, can you tell us the average funding reduction from approved levels by Institute?

Dr. Varmus: Although an overall rate of reduction for research project grants (RPGs) can be calculated using a simple comparison of initial review group recommended levels to awarded levels, this would not accurately reflect grant funding situations. NIH now uses policies outlined in "A Plan for Managing the Costs of Biomedical Research," the NIH Cost Management Plan (CMP), in funding RPGs. Before the CMP was developed, Institutes' funding policies typically called for across-the-board reductions of specified percents below recommended levels in order to support a targeted number of grants. In that situation, reporting levels of downward negotiations was clearly meaningful. Now, as suggested by the Committee, the CMP directs Institutes to utilize various strategies to manage increases in grant costs in order to achieve an average cost increase which does not exceed the amount of the Biomedical Research and Development Price Index (BRDPI) over the previous year. Recommended strategies include consideration of the costs of applications of equal merit in selecting grants for funding and negotiations of individual grants, if necessary, to ensure that the average cost increases of each Institute's RPG portfolio do not exceed CMP guidelines. Formulaic reductions are not used. The CMP directs that NIH replace formulaic across-the-board downward negotiations with rational scientific and administrative choices to fulfill NIH's grant funding strategy.

ADMINISTRATION OF DISEASE AREA FUNDING

Mr. Porter: Dr. Varmus, AIDS is not the only disease that is funded in multiple Institutes. Would the consolidated planning and budgeting process conducted by Dr. Paul's office for AIDS be a useful model, perhaps in a more informal way, for other diseases?

Dr. Varmus: Indeed, AIDS is not the only multi-Institute disease; however, AIDS is unique in that it is the only disease we can identify which spans the activities of every NIH Institute and Center. Although there are other diseases for which research crosses Institutes, in most cases only five or six Institutes or Centers support research for those diseases. In those cases, informal coordination is achieved at the program management level. Because of the magnitude of the HIV/AIDS research program at the NIH, the OAR plays a vital role in planning and coordinating AIDS research.

RFAS VS. INVESTIGATOR-INITIATED RESEARCH

Mr. Porter: Dr. Varmus, the various disease groups often press us to encourage you to issue requests for applications (RFAs) with directed funding for their disease. I know this tension between investigator-initiated research and NIH-directed research comes up from time to time, most recently in AIDS research. How would you advise us to handle this issue?

Dr. Varmus: The NIH has a range of programming tools for assuring that programs are developed properly. As part of its ongoing reviews and reinvention activities there is a committee reviewing how best to achieve program goals using all available tools. RFAs are an important means of achieving some of these goals but are not always the best mechanism. If there is a particular concern about a given disease problem, the whole range of programming approaches should be considered to evaluate and fill the needs.

Mr. Porter: Do you think NIH is putting too much money into RFAs?

Dr. Varmus: The RFAs are used judiciously by the ICDs. Reviewing the current status, it appears that the amount of funds assigned to RFAs is appropriate.

Mr. Porter: For the record, please provide the percentage of the extramural portfolio that is allocated by RFAs by Institute?

Dr. Varmus: The percentage of the competing Research Project Grant (RPG) budget awarded through RFAs between FY'86 and FY'94 is shown on the attached table for NIH as a whole and the individual Institutes and Centers.

% OF COMPETING RPG BUDGET IN RFAS, FY'86-'94

	NIH	AA	AG	AI	AR	CA	DA	DC	DE	DK
FY 86	4.9	4.6	10.8	10.6	0	7.1	0	0	0	2.0
FY 87	9.6	5.5	5.8	37.6	2.4	8.1	22.6	0	0	4.6
FY 88	9.3	4.8	9.8	31.2	0	4.5	18.6	0	3.4	8.5
FY 89	7.4	0.5	4.9	19.6	0	9.7	7.9	0	0	5.3
FY 90	8.8	29.8	12.8	23.0	4.6	12.3	8.2	5.3	10.7	4.2
FY 91	10.5	10.8	28.2	28.5	15.6	14.1	0.6	1.0	0	6.6
FY 92	14.5	13.5	17.8	45.4	1.0	13.5	0	4.5	2.9	13.6
FY 93	12.8	0	12.1	38.6	13.8	16.5	7.4	0	0	20.0
FY 94	14.5	18.9	7.9	30.2	17.3	15.8	10.3	2.1	11.2	27.6
	ES	EY	GM	HD	HG	HL	MH	NR	NS	RR
FY 86	1.4	4.9	0	9.3	0	9	0	0	0.2	0
FY 87	12.7	0.1	4.1	4.6	0	12.1	0.5	5.7	0	0
FY 88	0	2.6	3.9	17.2	0	11.6	1.8	7.8	3.5	0
FY 89	0	0	4.6	15.2	0	9.5	5.8	0	0	0
FY 90	0	0	1.0	10.0	1.8	6.5	2.3	5.1	0	34.1
FY 91	4.5	0	0	11.6	40.6	7.8	1.7	9.2	3.0	44.0
FY 92	54.2	0	3.1	11.4	16.4	12.6	1.3	26.2	1.2	0
FY 93	11.2	0	0	12.1	7.2	12.3	1.7	27.8	0	0
FY 94	20.1	0	0.1	23.2	8.2	15.1	16.2	34.8	2.3	0

GLOSSARY

AA - National Institute on Alcohol Abuse and Alcoholism
AG - National Institute on Aging
AI - National Institute of Allergy and Infectious Diseases
AR - National Institute of Arthritis and Musculoskeletal and Skin Diseases
CA - National Cancer Institute
DA - National Institute on Drug Abuse
DC - National Institute on Deafness and Other Communication Disorders
DE - National Institute of Dental Research
DK - National Institute of Diabetes and Digestive and Kidney Diseases
ES - National Institute of Environmental Health Sciences
EY - National Eye Institute
GM - National Institute of General Medical Sciences
HD - National Institute of Child Health & Human Development
HG - National Center for Human Genome Research
HL - National Heart, Lung, and Blood Institute
MH - National Institute of Mental Health
NR - National Institute of Nursing Research
NS - National Institute of Neurological Disorders and Stroke
RR - National Center for Research Resources

HUMAN EMBRYO RESEARCH

Mr. Porter: Regarding the "sensitive subject" of human embryo research, the Clinton moratorium seems to contradict part of the Panel's recommendations. How will you resolve this?

Dr. Varmus: On December 2, 1994, the President issued a statement directing that NIH not allocate any resources to support the "creation of human embryos for research purposes." This directive is binding on the Executive Branch, and it will remain in effect unless and until it is reversed by the President or by statute. The directive means that NIH may not fund research that involves an embryo, i.e., a human egg fertilized in vitro, expressly for research purposes, where there is no direct therapeutic intent. The directive does not apply to research involving human eggs fertilized in vitro for treatment purposes, whether the resulting preimplantation embryos are actually used in treatment or whether they are remaining when treatment is completed. What remains to be resolved or decided is whether the NIH should proceed with the funding of research involving human eggs fertilized *in vitro* for treatment purposes.

Mr. Porter: When can we expect a decision?

Dr. Varmus: I am currently reviewing the recommendations of the Panel that relate to the research not affected by the President's directive and will reach a decision in the near future about how I think we should proceed. I can say at this point that I firmly agree with the Panel and the Advisory Committee to the Director that an ad hoc advisory group should be formed to monitor ethical and scientific issues associated with this research on a continuing basis, to promote public understanding of the research, and to review all research proposals involving human IVF before funding is finally permitted.

Mr. Porter: Regarding indirect costs, the Administration has proposed moderate cuts. Some, however, would call for NIH to be a "prudent purchaser" and suggest that NIH only make awards to institutions with lower indirect cost rates. Please comment.

Dr. Varmus: The Administration has proposed several modifications to OMB Circular A-21 that will have a constructive effect on the stabilization and streamlining of indirect costs. However, the changes do not represent actual reductions of indirect costs payments in FY 1996. Certain changes will have a positive economic effect over the next several years, such as the elimination of special studies for the determination of utility costs, the elimination of dependant tuition benefits, and the requirement to use the rate in effect at the time of the award throughout the life of the project.

NIH actively engages in effective cost management practices, as a "prudent purchaser". Reductions are often made in project budgets based on the recommendations of reviewers, staff cost analysis, or staff judgements about affordability. However, as a "prudent purchaser", NIH must take into account the merit of the scientific project, the type of science, and its contribution to its overall program portfolio. There are very few occasions that NIH can select projects based on the organization and its indirect cost rate.

Mr. Porter: In returning the three ADAMHA Institutes to NIH, the Congress directed that 15 percent of the research budget of each agency be set aside for research on health services. Please briefly update the Committee with respect to ongoing services research activities and how you plan to continue to implement this part of NIH's public health mission.

Dr. Varmus: The three former ADAMHA Institutes (the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA)) are required under the provisions of P.L. 102-321, to obligate no less than 15 percent of the funds appropriated to them each year for the support of health services research. The Institutes have been extremely successful in stimulating an outstanding response from their fields in services research to conform to this Congressional mandate, as indicated below:

NIMH:

Development of the NIMH services research program is guided by two multi-year strategic plans based on extensive input obtained from panels of outside experts and consultants: the National Plan for Research on Child and Adolescent Mental Disorders (1990) and Caring for People with Severe Mental Disorders: A National Plan of Research to Improve Services (1991). Some notable recent accomplishments of the NIMH services research program include:

* Launching of a four community site project, known as the Mental Health Service Use, Need, Outcomes, and Costs in Child and Adolescent Populations (UNO-CAP) study. UNO-CAP will provide a detailed look at the characteristics of the mental health service system and how services are both provided to and used by children across six major service sectors -- mental health, general health, education, child welfare, juvenile justice, and substance abuse.

* Multi-year development of research findings on the economic costs of mental illness and the utility of different options for financing mental health services. Data from NIMH services research was a key component of a 1993 report to the Senate Committee on Appropriations concerned with the cost of providing insurance coverage for the medical treatment of severe mental illness on a scale commensurate with current coverage of other illness. The conclusion was that a net economic benefit of $2.2 billion, primarily in indirect costs, to the nation could be achieved.

* Support for the Medical Outcomes Study (MOS), a 2-year longitudinal study of variations in practice style and outcomes of care for patients with specific chronic conditions, one of which was depressive disorder. The MOS focused on a large sample of adults who received care in three U.S. cities (Boston, Chicago, Los Angeles) in one of three systems of care: HMOs, large multispecialty group practice, and solo practice providers and single-specialty small groups. Findings from this study on clinical practice for depressive disorders have been widely reported in the Journal of the American Medical Association (JAMA) and other leading journals.

Research findings that a majority of depressed patients seen in primary care settings experience recurrent depression which places them at elevated risk for disability, high health care utilization and costs, family dysfunction, suicide attempts, and suicide. Co-management of depressed patients by a primary care physician and a mental health professional significantly improved treatment outcomes.

* Research findings with implications for Medicaid, one of the largest payors for mental health services. An NIMH study found that cost-containment measures limiting the access of schizophrenic

patients to medications can cost more money than they save. For example, a cap on Medicaid reimbursement, limiting patients to three prescriptions per month, resulted in immediate reductions in the use by schizophrenic patients of antipsychotic drugs and other psychotropic drugs for co-occurring disorders and (as a serious negative consequence) a coincident increase in both the number of visits patients made to community mental health centers and in their use of emergency mental health services. The average resulting increase in costs per patient was $1,530 -- 17 times more than the reduction in Medicaid drug costs while the cap was in place.

New initiatives planned by the NIMH services research program in FY 1995 and beyond include a program announcement designed to encourage more research on the quality of care and outcomes; increased attention on research regarding mental health services for the elderly; and research aimed at the development of improved methodologies for conducting mental health services research.

NIDA:

NIDA sees health services research as a critical research component because of its ability to answer questions about the cost-effectiveness of drug abuse treatment services; the effects of public and private financing and coverage on drug abuse treatment outcomes, service delivery and utilization; and approaches for altering the practices of drug abuse practitioners and other health care providers. Accordingly, NIDA supports a significant portfolio of research on the organization, financing, and management of health services and their impact on the quality, cost, and outcomes of care both within established service delivery settings and at a systemwide level. Activities include:

* NIDA has undertaken a variety of activities to stimulate drug abuse health services research, including issuing new program announcements; initiating a formalized health services research planning process, and collaborating with other Federal agencies and professional organizations.

* NIDA has engaged in an intensive grant stimulation effort which has resulted in 20 new grants in the health services research area that were funded in 1994.

* A request for applications (RFA) to establish health services research centers was recently issued. Immediate plans call for the establishment of health services research centers to be awarded this year. These centers will provide stable, interdisciplinary research environments that will attract leading investigators in the behavioral, social, and economic sciences to conduct research focused on the impact of health services financing, organization and management on the quality of drug abuse services.

* A program announcement (PA) on Drug Abuse Health Services Research and HIV/AIDS has been issued, and a NIDA-sponsored conference on managed care for substance abuse will be conducted to develop and stimulate future health services research. In addition, NIDA published a notice in the NIH Guide to Grants and Contracts designating health services research as a top priority in the funding of research training grants in FY 1995.

NIAAA

* For NIAAA, health services research is a logical outgrowth of their other research domains. The goal of NIAAA's health services research program is to develop a knowledge base in four areas: 1) financing and reimbursement; 2) effectiveness and client/patient outcomes; 3) utilization costs; 4) delivery system organization and management. The knowledge generated by this program of research can

guide development of public and private sector policies for the provision of efficient and effective services for the treatment and prevention of alcoholism, alcohol abuse, and alcohol-related problems.

* In order to stimulate high quality research applications, NIAAA has reissued a Request for Applications targeting health services research for FY 1995 and FY 1996. In addition, NIAAA's National Advisory Council has initiated the development of a national plan for alcohol-related health services research to provide outside expertise to the Institute on the appropriate and most promising areas of research to be pursued.

Mr. Porter: Can you briefly describe for us your view of the importance of clinical research supported by NIH and its translation into patient care, using the example of manic-depressive disorder as an example?

Dr. Varmus: NIH clinical research has been the foundation for clinical innovations and new treatments for a wide variety of diseases and disorders. Research on manic-depressive disorder is supported by the National Institute of Mental Health (NIMH), which continues to fund such studies to improve the efficacy of treatments available to the mentally ill. Most of this research has been devoted to carefully controlled studies in which specific forms of intervention, such as psychotherapy, or drugs, are applied and evaluated. Caring for People with Severe Mental Disorders: A National Plan of Research to Improve Services (1991), the NIMH plan for services research, identified priorities for clinical and rehabilitative care research that included: (1) Assessment--Developing accurate and comprehensive tools to guide clinical management and rehabilitation services for individuals.
(2) Treatment and Rehabilitation--Evaluating the provision and integration of medication, psychosocial intervention, and rehabilitation into an overall plan. (3) And Outcome--Measuring the benefits of treatment packages across a full range of dimensions, including quality of life and cost in relation to outcome. Clinical studies are the only way to find which treatments work for which people, and with the fewest side effects.

Manic-depressive or bipolar affective disorder affects approximately 1.3 percent of the U.S. population at some time during their lives, according to the NIMH Epidemiologic Catchment Area Study. The disorder is recurrent and, left untreated, an individual patient could experience at least ten major episodes of depression and/or mania. The overwhelming majority of all adolescents and adults who commit suicide suffer from either bipolar or major depressive illness. Manic-depressive disorder is treatable with lithium carbonate, although approximately 40-50 percent of patients are either nonresponsive or cannot tolerate its side effects. Lithium may also reduce, but not eliminate, symptoms in many, leaving the patient with a functional deficit. Despite its shortcomings, it has been estimated that the use of lithium carbonate to treat manic-depressive illness has saved the Nation $39 billion in lost productivity and in other costs related to this debilitating chronic illness over just the past 20 years. The savings from this one treatment--whose widespread adoption in the U.S. was stimulated by systematic NIMH clinical studies demonstrating its safety and efficacy--are 10 times greater than the total expenditures for all NIMH research ($3.9 billion) during the same 20-year period.

Researchers in the NIMH Intramural Research Program (IRP) have pioneered the use of new medications in the treatment of bipolar disorder. IRP staff were instrumental in the approval of lithium to treat bipolar disorder. NIMH researchers also have discovered new biological mechanisms through which lithium seems to work. These mechanisms had largely remained a mystery since lithium's introduction in 1970, and their discovery may pave the way for the development of new, more effective medications in the years to come. More recently, Dr. Robert Post of the Biological Psychiatry Branch has shown the utility of the well-known anticonvulsant drug, carbamazepine, in both acute mania and in the prevention of relapse. An NIMH grantee, Dr. Charles Bowden, has reported that another previously approved anticonvulsant drug, valproate, is also safe and effective in the treatment of bipolar disorder. Based on this work, a Food and Drug Administration advisory committee has recently approved valproate for this new indication.

Intramural investigators in the Biological Psychiatry Branch have identified and assessed two subgroups of patients with ultra rapid cycling periods. These patients who demonstrate distinct oscillations in mood within a 24-hour period, are inadequately responsive to traditional therapies including lithium, carbamazepine, and valproate. In light of this increasingly severe pattern of illness based on cycle frequency, scientists are exploring other treatment modalities such as calcium channel blockers, including the anticonvulsant calcium channel blocker nimodipine.

Another study by Dr. Ellen Leibenluft in the IRP Clinical Psychobiology Branch concentrates on rapid-cycling bipolar disorder. These patients experience at least four episodes of affective illness (depression, hypomania, and/or mania) in a year and are frequently resistant to conventional treatments. Bipolar women are three times more likely than bipolar men to develop a rapid-cycling course. Therefore, this illness warrants study because of its significant morbidity and because it can yield information about the effects of gender on the course of bipolar disorder.

Other NIMH extramural and intramural researchers are looking for genetic markers for bipolar disorder and have found several promising leads. The genetic basis for the disease is very important because it might point the way to the primary biological dysfunction which contributes to the development of this disorder. By understanding the primary biological cause, new treatments can be designed that are more specific and effective.

NEUROFIBROMATOSIS RESEARCH

Mr. Obey: Dr. Varmus, I believe you are aware that I have been concerned about research in the area of neurofibromatosis for several years. This is based partially on personal knowledge of a number of cases of this disease presented at our hearings but it is also based on my concern that this research, despite its potential, has not been well coordinated among the various NIH Institutes. While NINDS has been the theoretical lead institute in this area, NCI seems to give NF a higher priority. I am sympathetic to the suggestion of several of the advocacy groups that the lead responsibility be transferred to the Cancer Institute. Would this in your view be an appropriate organization change?

Dr. Varmus: The neurofibromatoses (NF) are genetic disorders that primarily affect cell growth of neural tissues. As such, they are primarily neurological disorders treated by neurologists and belong within the portfolio of the National Institute of Neurological Disorders and Stroke (NINDS) which continues to be the key NIH component providing leadership on neurofibromatosis research. These disorders can cause tumors to grow on the nerves, and in this regard are also of interest to scientists in and supported by the National Cancer Institute (NCI). The NINDS and the NCI have jointly issued a Program Announcement encouraging grant applications concerning neurofibromatosis, and staff from the two Institutes work together cooperatively concerning project review and funding issues. Several other manifestations of the NF disorders have impact on other systems of the body that are of interest to other NIH components. For example, as NF affects vision and hearing, the National Eye Institute and the National Institute on Deafness and Other Communication Disorders also have scientific interest. While aspects of NF span many areas of scientific interest to several NIH components, the NINDS remains the appropriate focal point of strongest research interest and progress. NINDS personnel meet regularly with members of the NF voluntary organizations. In June 1994, NINDS staff met with representatives of the National Neurofibromatosis Foundation to discuss research issues and ways of promoting research interest in the disease. The NINDS extramural staff person responsible for neurofibromatosis attended the 1993 National Neurofibromatosis Foundation meeting in Ann Arbor, Michigan, and the Neurofibromatosis Satellite Symposium in October 1994, held in conjunction with the Annual Meeting of the American Society of Human Genetics. In January 1995 the new Director of the NINDS, Dr. Zach Hall, met with National Neurofibromatosis Foundation representatives. The NINDS continues to vigorously promote research on neurofibromatosis, and provide a focal point within NIH for the disease. Changing the organizational focus would not be appropriate.

Mr. Obey: Also, tell us what actions are planned to stimulate more interest in NF studies in the research community.

Dr. Varmus: NINDS and NCI together issued one Program Announcement encouraging grant applications on Neurofibromatosis in 1992, and NINDS issued a second one on Neurogenetic Disorders of Infancy and Childhood including the neurofibromatoses in 1994. These Program Announcements notify the scientific community of continuing NIH interest in the submission of research grant applications concerning NF. NINDS intramural scientists are using nuclear magnetic resonance and positron emission tomography imaging to assist in defining and classifying tumors of the nervous system, such as in NF. This effort will greatly assist other scientists in the field, since there are many manifestations and sub-types of NF that have thus far eluded precise definition. Due to the enormous progress in NF research through NIH-sponsored studies, the current situation is one of great opportunity. NF remains an important area of research for the NINDS and other contributing NIH components.

Mr. Obey: The report on NF research submitted to this Committee two years ago was considered inadequate by many of the advocates for research in this area. Would you submit to the Committee within the next 45 days an updated report showing all studies in this area and a description of the coordination structures which are in place.

Dr. Varmus: We would be pleased to submit an updated report to the Committee. NF research in the past few years has been flourishing, and there are several new findings to report. I am sorry to hear that some advocates for research in this area considered the report submitted to the Committee two years ago to be inadequate. Most respondents, including the oldest and largest of the two private voluntary agencies, associated with NF were pleased by the report. The three major items of concern were related to projects sponsored by the National Cancer Institute, the National Center for Human Genome Research (NCHGR), and the National Institute of Child Health and Human Development (NICHD), respectively. The NCI was one of the major contributors to the report and included a description of its significant, applicable research in the report. The NCHGR is now supporting a small grant project to sequence the region near the NF 1 gene. However, this project was not supported during the period covered by the report. Finally, the NICHD study is, in fact, not a research project investigating NF; it is a major program project studying learning disabilities. One arm of the larger program project has some enrolled subjects who have NF, but the fact they have NF is not the focus of the study.

Mr. Obey: Since Dr. Roswell Eldridge retired two years ago, there is concern that the clinical expertise on NF at the Clinical Center has declined. What are your current capacities in this area within the intramural program?

Dr. Varmus: Clinical applications must be preceded by scientific understanding. The NINDS alone is responsible for over 600 disorders. Obviously, it is not possible for the Institutes to have intramural scientists who devote their research specifically to each of these diseases. Therefore, NINDS tries to structure its intramural research program to address broad issues, the findings of which will have wide benefits. For example, NINDS intramural scientists are using nuclear magnetic resonance and positron emission tomography imaging to assist in defining and classifying tumors of the nervous system, such as those that occur in NF. This effort will greatly assist fundamental and clinical scientists in the field, since there are many manifestations and sub-types of NF that have thus far eluded precise definition.

Mr. Obey: Will additional personnel with NF expertise be hired?

Dr. Varmus: Although this is a time in which the NIH must engage in efforts to streamline rather than expand its intramural program, it is fortunate that this process does not present a problem for NF research. The highly successful products of previous and recent NIH conducted and supported studies have moved the research into areas that are heavily investigated by many scientists throughout the country. These include identification of the protein products of the NF genes and their distribution, functions, and relationships to various cell types and tissues and the cellular and physiologic processes occurring at these sites.

Mr. Obey: Does NIH plan to reactivate the NF Research Committee established several years ago to monitor, coordinate and stimulate research in this area?

Dr. Varmus: In its report on the Fiscal Year 1993 budget for the Department of Health and Human Services, the Committee on

Appropriations of the House of Representatives recommended the establishment, on a temporary basis, of a neurofibromatosis (NF) research coordinating committee at the NIH to ensure the development of NF research plans within the relevant components and an overall plan to coordinate and integrate such research. The Committee requested that a report on current NF research at NIH be prepared and submitted. NIH established a temporary Neurofibromatosis Research Coordinating Committee (NRCC) which held quarterly meetings and produced a report in January 1993 that included the activities of the National Institute of Neurological Disorders and Stroke, the National Cancer Institute, National Eye Institute, National Institute on Deafness and Other Communication Disorders, and the National Center for Research Resources. It was found that the existing mechanisms in the Division of Research Grants, utilized by all NRCC components, are both efficient and useful. The research and funding mechanisms of the NIH promote coordinated research on NF in the following ways: (1) Great care is taken through the use of referral guidelines to assure that research grant applications are assigned to the institute or center with the closest match in terms of mission. (2) Institutes may invite the participation of other NIH components to participate in solicitations for grant applications. All planned institute solicitations are circulated to the other components allowing for the possibility of cosponsorship. For example, in 1992, a solicitation for grant applications concerning NF was cosponsored by the NINDS and the National Cancer Institute. (3) Collaborations between institutes' intramural branches and laboratories occur when parallel scientific lines of inquiry develop. Taken together, it is felt that these utilized mechanisms provide ample means for coordination and collaborative inquiry, and reactivation of a coordinating committee is not necessary.

EFFECT OF FEDERAL DOWNSIZING ON SENIOR SCIENTIST POSITIONS

Mr. Bonilla: NIH, like all federal agencies, is under a mandate to cut civil servants holding the rank of GS-14 and above. The goal of this mandate is to cut bureaucrats at federal agencies, which we all certainly support. But I understand that this government-wide effort is having unintended consequences in that doctors who are doing research are being forced out at the NIH, not just bureaucrats. Is this understanding of the situation correct?

Dr. Varmus: NIH, by the nature of its mission, has a higher-than-normal senior grade structure because it employs large numbers of professional staff such as doctors, scientists and researchers, chemists, epidemiologists, etc., that command salaries at senior level grades because of their scientific and technical expertise. In order to protect highly paid PHS scientists, doctors and researchers who are not management or administrative positions, HHS requested from OMB an initial exemption from the requirement to reduce senior level positions by 10 percent of the total HHS reduction. On March 22, 1994, OMB informed HHS that it agreed with HHS's analysis of the situation and has granted the requested exemption. This exemption removes 2,310 senior-level FTEs from the HHS senior-level FTE base.

Mr. Bonilla: Recognizing that government must be downsized, is there a better way to do this at NIH?

Dr. Varmus: The NIH believes that limiting senior level staff reductions to supervisory and managerial positions is consistent with the goals of the National Performance Review.

HIGH COST OF DEVELOPMENT OF ANIMAL MODELS

Mr. Miller: Costs of Research, Costs of Animals in Research: This Subcommittee has heard much about the great research that is being done using, for example, genetically-altered mice. The use of such mice has led to recent advances in such autoimmune diseases as spinal arthritis, diabetes, and Alzheimer's Disease.

Yet, we hear from researchers that the rising costs of doing research with such mice is effectively preventing us from pursuing these promising discoveries. Do you have any comments or advice for the Subcommittee in addressing this problem?

Dr. Varmus: Transgenic mice have proven to be extremely powerful models for defining specific gene function and defining the molecular basis of many important human diseases. The cost of developing and maintaining transgenic mice can be expensive. The estimated cost of generating founder stock of transgenic mice costs on average $3,000 per line. In some laboratories in which many lines must be developed, the cost rapidly multiplies. Additional very substantial costs are associated with maintaining the lines. Investigators may need to keep 250 to 100 mice per line at a cost of approximately $50 to $100 per day. The caging of those animals must comply with the Guide for animal housing.

In an effort to decrease these costs, the National Center for Research Resources (NCRR) established a national resource for the production and validation of transgenic mice at the Jackson Laboratory, Bar Harbor, Maine. This resource cryopreserves and "banks" selected valuable strains of mice as frozen embryos and makes the animals available to investigators at a modest fee. That approach helps control the expense for developing transgenic mouse lines. The demand on Jackson Laboratory resource has been substantial and, as a result, the NCRR is expanding that resource capacity.

QUALITY OF RESEARCH FUNDED BY SBIR SET-ASIDES

Mr. Miller: SBIR: As you know, the SBIR (Small Business Innovation Research) Program is funded by a set-aside from dollars appropriated for basic, biomedical research at the NIH. We have heard testimony to the effect that this percentage will rise from 1.5% to 2.1% by Fiscal Year 1996 (a 41% increase) and that in Fiscal Year 1995, $162.6 million will be taken out of the pool that would otherwise fund basic research.

Do you have any comment on the quality of the research funded by SBIR when compared to investigator-initiated research grants?

Dr. Varmus: The SBIR program, which was authorized initially by P.L. 97-219, dated July 22, 1982, and amended by P.L. 99-443, dated October 6, 1986, was reauthorized by P.L. 102-564, dated October 28, 1992, the "Small Business Research and Development Enhancement Act of 1992." Each Federal agency that has an extramural budget in excess of $100 million participates in the SBIR program. Among other provisions, the 1992 Act expanded the SBIR program through Fiscal Year 2000 by incrementally increasing the percentage of the extramural budget reserved for the program from the previous level of 1.25 percent from Fiscal Years 1987-1992 to:

Fiscal Years 1993-1994:	1.5 percent (a 20 percent increase)
Fiscal Years 1995-1996:	2.0 percent (a 33 percent increase)
Fiscal Years 1997-2000:	2.5 percent (a 25 percent increase)

The estimated amount to be set-aside by the NIH for the SBIR program in Fiscal Year 1995 is $173.4 million. The SBIR grants funded by the NIH are investigator-initiated research grants and are included within the "research project grants" line of the budget. As required by the 1992 Act, the General Accounting Office (GAO) has reported recently on the quality of research proposals for technological innovation submitted to the five largest SBIR agencies by small business concerns. These five, Department of Defense, Department of Health and Human Services (NIH), Department of Energy, National Aeronautics and Space Administration, and the National Science Foundation, provide over 90 percent of the funds for the SBIR program. In its report, GAO/RCED-95-59, entitled "FEDERAL RESEARCH: Interim Report on the Small Business Innovation Research Program," dated March 8, 1995, the GAO comments that "the quality of research proposals has kept pace with the program's expansion."

Mr. Miller: Is this the way you would spend research dollars if the decision were up to you?

Dr. Varmus: The NIH believes that its portfolio of research opportunities should include those that have, as their primary purpose, the commercialization of the subject of the research. As a nation competing in a global economy, the United States depends heavily on innovation through research and development (R&D). Because small business concerns have been identified as a principal source of significant innovation, the SBIR program strengthens the role of small, innovative companies in Federal R&D.

HIV/AIDS PREVENTION EFFORTS

Mr. Dickey: Although there is not yet a vaccine to prevent HIV infection, it seems we have discovered specific behaviors that can eliminate the spread of HIV, specifically the avoidance of unprotected sexual relations and intravenous drug abuse. If a man or woman is responsible enough not to become a member of one of these groups, what are his or her chances of becoming infected with HIV?

Dr. Varmus: HIV is an infectious agent. As such, it is important not to underestimate its ability to move from person to person and from group to group in ways that are more complex than the simple engagement in or avoidance of particular behaviors. Although it is possible to identify populations most at risk of contracting HIV/AIDS, and it is possible to minimize the potential of transmission among individuals through changing sexual and drug-using behaviors and by ensuring a clean blood supply, the virus knows no population boundaries. It is therefore difficult, if not impossible, to estimate any individual's chance of becoming infected with HIV. It is important to continue social and behavioral research that has begun to uncover the mechanisms by which the virus moves from population group to population group through individuals who are members of different social networks within these groups. Knowledge from social and behavioral research and information gained from natural history studies will assist us in designing more effective HIV/AIDS prevention interventions.

Mr. Dickey: What percentage of your HIV/AIDS resources are used to promote these behaviors that seem to virtually eliminate the spread of HIV?

Dr. Varmus: In FY 1996, it is estimated that 8.4 percent of the AIDS budget for NIH is allocated to the category of Behavioral Research; that is, research that most directly addresses understanding and preventing the behaviors that contribute to the transmission of HIV. However, behavior-related research is included in several other categories of the NIH AIDS Plan. For example, Natural History and Epidemiology research includes population-based studies of sexual and drug-using behaviors. Therapeutics, as well as Vaccine research, includes research on individuals' adherence to clinical treatments and participation in clinical trials. The Institutes, Centers, and Divisions (ICDs) determine the classification for each project, and in cases where projects have both behavioral and biomedical components, coding of the projects may not indicate the behavioral component. Research on the behaviors associated with transmission of HIV represents at least 8.4 percent of the NIH AIDS budget. However, this figure is actually much higher for the total behavioral research portfolio that is included in other categories of the Plan.

Mr. Dickey: Studies I have seen show that cardiovascular diseases, including ischemic heart disease, acute myocardial infarction, and congestive heart failure are the leading cause of death among all Americans, yet the funding level for heart research is a fraction of the funding level for cancer and HIV/AIDS research. Why does that discrepancy exist?

Dr. Varmus: In order to put this apparent discrepancy in perspective, one must consider the overriding factor that HIV/AIDS is an infectious disease. Although the first case of AIDS was recognized in 1981, AIDS has already become the leading cause of death among Americans aged 25-44. The number of deaths from AIDS is increasing each year in the United States as well as in other parts of the world. This constitutes a pandemic of unforeseeable proportions. In fact, the United States faces not one, but several AIDS epidemics. Today, the epidemic among older homosexual and bisexual men has leveled, reflecting in part the effect of targeted prevention efforts. But researchers at the National Cancer Institute (NCI) estimate that one-quarter of all new infections occur among young people under the age of 22, and fully one-half of new infections occur among people under 25 years of age. NCI researchers also have shown that the time from infection to AIDS in these younger persons is longer than in older persons. Therefore, the size of the "HIV iceberg" is growing, and these are AIDS cases that have yet to be diagnosed. In addition, the proportion of cases among heterosexual men, women, racial and ethnic minorities, and children continues to increase. Infectious diseases are unpredictable, and may sometimes appear to be contained for some periods of time. However, for reasons unknown, the infectious agent will reemerge with high rates of transmission. History has shown that complacency about infectious diseases can be dangerous. Research plans are generally not developed based on mortality rates, but rather on scientific opportunities and public health emergencies.

DETERMINING FUNDING LEVELS FOR DISEASE AREAS

Mr. Dickey: What criteria do you take into account when determining funding levels for the research of different diseases?

Dr. Varmus: At the NIH, decisions on funding levels for the research of different diseases reflect a combination of judgments about scientific opportunity and national priorities. On the broadest level, we receive direction from Congress during the appropriations process and in periodic reauthorization legislation. In addition, we obtain guidance from the Administration, and from NIH constituent Institutes, Centers, Divisions (ICDs) as well as various NIH advisory committees that form the decisionmaking of the agency throughout the year. Through those channels of advice flow the many diverse viewpoints of the American people and of concerned groups about what research should receive priority for funding.

In addition to these directives and inputs regarding priority areas of research, NIH strives to allocate research funding on the basis of scientific advances and opportunities. To that end, we support a substantial number of investigator-initiated proposals through grants to the extramural research community. In my view, the greatest and most influential discoveries have usually been the products of young minds free to think creatively about the natural world. This is especially true in the basic research supported and conducted by NIH since tangible results of scientific inquiry cannot always be defined or planned in advance. Consequently, while society may desire that a specific goal be attained within a certain time frame, such as “a cure for arthritis”, a lack of knowledge regarding underlying physiological processes about the disease may need to be addressed before diagnostic and therapeutic technologies can be developed and evaluated. At the same time, a recent research advance in another area may create unplanned and unexpected new scientific opportunities for R&D, including further diagnostic and therapeutic applications.

Finally, as a public health agency, NIH regularly considers the critical public health threats of various diseases, such as AIDS and tuberculosis, in its research decisions and mobilizes resources appropriately to address these concerns.

Mr. Dickey: I have been very interested in the Human Genome Project and the beneficial consequences of that research. I have also become concerned with the possible consequences of a misuse of that research. To what ethical standards do the NIH scientists adhere in order to assure a proper use of the genetic research?

Dr. Varmus: The NIH shares your concerns about the possible misuse of genetic information that may result from the participation in genetics research. As a result, the National Center for Human

Genome Research has established the Ethical, Legal, and Social Implications (ELSI) Branch and spends not less than 5 percent of its total budget addressing these important issues. The ELSI Branch has established four priority research areas: ethical issues in genetics research, the responsible clinical integration of new genetic technologies, privacy and fair use of genetic information, and public and professional education. As a result of its efforts, the ELSI Branch is influencing the development of new recommendations regarding informed consent, privacy and confidentiality related to participating in genetics research. Most recently, the ELSI Branch has supported the development of an interagency document which makes specific recommendations regarding informed consent for genetics research using stored tissue samples.

BIOETHICS AND GENETICS

Mr. Dickey: After important genetic discoveries are made, how will we extend ethical principles to others who wish to use the new genetic information in an unethical manner?

Dr. Varmus: Perhaps the greatest risks associated with learning genetic information about ourselves at the present time is the possibility that it will be misinterpreted or misused. One area in which genetic information may be misused is in the area of health insurance. At the present time individuals who have or are suspected to have a genetic predisposition to develop a disease may experience health insurance discrimination. In the current system, people with pre-existing conditions and genetic predispositions to disease may see their insurance rates increase, their existing policies cancelled, or experience difficulty in obtaining new life or health insurance policies. But we all carry genetic predispositions to one illness or another, and over time more and more of us will be able to learn this information. Perhaps the best way to ensure that such information is not misused in this way is through reform of the health insurance system to reduce the likelihood that insurance discrimination based on one's genotype will occur. To further protect individuals, legislation to protect people from employment discrimination based on genotype and to protect every individuals' genetic privacy may be necessary.

HISTORY OF RPG SUCCESS RATES

Mr. Stokes: The total number of Research Project Grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the FY 1996 budget would support a success rate of 23 percent. If we look at five year increments, to what extent has the success rate remained relatively flat over the past five to ten to fifteen years, explain.

Dr. Varmus: Numbers of research project grants (RPGs) grew steadily from 19,710 in FY 1985 to 22,725 in FY 1989. Since FY 1992, numbers of RPGs have remained fairly constant at approximately 24,000 grants.

From FY 1985 to FY 1994 the number of submitted competing applications has increased by 24 percent. Success rates for NIH in total have fluctuated from a high of 32 percent to a low around 23 percent. NIH's overall success rates are estimated to be 24 percent and 23 percent, respectively, in FY 1995 and FY 1996 indicating a slight decline.

SUCCESS RATES FOR MINORITY AND WOMEN RESEARCHERS

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Varmus: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NIH is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Also, on average, approximately 5 percent of grant applicants choose not to complete the portion of the grant application referring to race and gender and have been coded in the "unknown" category. There is no way to predict the race or gender composition of those applicants. Thus, the following data may not provide a true representation of NIH's support of minority and women researchers.

The following table lists success rates for minority researchers for FY 1994, including a category identified as "unknown" for those grant applicant who chose not to identify their ethnic origin and/or gender. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of women researchers:

Competing Grant Success Rates for Minority Researchers

Total NIH
Fiscal Year 1994

Asian	Afro-Amer.	Hispan.	Native Amer.	Unknown	White
19.8%	14.4%	21.0%	23.3%	29.7%	24.7%

Mr. Stokes. What is the success rate for research applications received from women?

Dr. Varmus: The following data identifies success rates for women researchers who chose to answer the optional questions on the grant application related to race and gender. A category denoted as "unknown" represents success rates for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of women researchers:

Competing Grant Success Rates for Women Researchers

Total NIH
Fiscal Year 1994

Female	22.9%
Unknown	38.4%

Mr. Stokes: What is the success rate for research applications received from African Americans?

Dr. Varmus: The following data identifies success rates for researchers of African American descent who chose to answer the optional questions on the grant application related to race. A category denoted as "unknown" represents success rates for applications in which race could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of African American researchers:

Competing Grant Success Rates for African American Researchers

Total NIH
Fiscal Year 1994

Afro-American	14.4%
Unknown	29.7%

SUCCESS RATES FOR HBCUS

Mr. Stokes. What is the success rate for research applications received from HBCUs?

Dr. Varmus: The following data identifies success rates for Historically Black Colleges and Universities:

Competing Grant Success Rates for HBCUs

Total NIH
Fiscal Year 1994

HBCUs	7.7%

HISTORY OF AVERAGE COSTS OF AWARDS

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period?

Dr. Varmus: The average annual cost of research project grants, in total, has increased approximately 5 percent over the 10-year period. Since the implementation of the Cost Management Plan (CMP) in FY 1991, however, the average increase has dropped to approximately 4 percent, roughly equal to inflation as measured by the Biomedical Research and Development Price Index (BRDPI). NIH anticipates that the average cost of all RPGs will continue to average inflationary increases, as set forth in the CMP.

Mr. Stokes: What does the trend look like in terms of constant dollars?

Dr. Varmus: In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average annual cost of research project grants, in total, has increased over the 10 year period by -.4 percent. This average annual cost increase drops to approximately -

.6 percent, slightly less than inflation, since FY 1991 and the implementation of the Cost Management Plan.

AVERAGE COST OF AWARDS FOR MINORITY AND WOMEN RESEARCHERS

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to women?

Dr. Varmus: The following data identifies the average cost of competing awards to women researchers in real and constant dollars. As stated previously, questions related to race and gender are optional on NIH grant applications. As a result, the following table identifies a gender category denoted as "unknown" which represents the average cost of competing grants for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of women researchers:

Competing Grant Average Costs for Women Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIH:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Women	$120.6	$120.6	$162.2	$133.8	$204.2	$135.7
Unknown	121.5	121.5	176.2	145.4	228.9	165.2

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to minority researchers?

Dr. Varmus: The following data identifies the average cost of competing awards to minority researchers in real and constant dollars. As stated previously, questions related to race are optional on NIH grant applications. As a result, the following table identifies a race category denoted as "unknown" which represents the average cost of competing grants for applications in which the ethnicity of the awardee is undetermined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of minority researchers:

Competing Grant Average Costs for Minority Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIH:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Asian	$121.8	$121.8	$159.9	$132.0	$185.7	$123.5
Black	165.1	165.1	185.4	152.9	157.1	104.5
Hispanic	141.0	141.0	208.1	171.7	189.4	125.9
N. Amer.	354.8	354.8	200.9	165.7	192.5	128.0
Unknown	144.0	144.0	186.3	153.7	234.1	155.6
White	145.5	145.5	187.3	154.5	225.9	150.2

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to African American researchers?

Dr. Varmus: As shown in the previous table, the average costs of African American researchers in constant and current dollars are as follows:

Competing Grant Average Costs for African American Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIH:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Black	$165.1	$165.1	$185.4	$152.9	$157.1	$104.5
Unknown	144.0	144.0	186.3	153.7	234.0	155.6

AVERAGE COSTS OF AWARDS FOR HBCUS

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to HBCUs?

Dr. Varmus: Average Costs of awards to Historically Black Colleges and Universities in current and constant dollars are as follows:

Competing Grant Average Costs for HBCUs in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIH:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
HBCUs	$266.6	$266.6	$78.5	$64.8	$252.4	$167.8

PERCENT OF COMPETING AWARDS BY RACE

Mr. Stokes: According to a November 1993 article appearing in the Chronicle of Higher Education, white scholars received 90 percent of the research grants awarded competitively by the National Institutes of Health in 1991, according to a study by the Agency. The study found that in the same fiscal year, Asians had received about 8 percent of such grants, Hispanics 1.5 percent, and African Americans 0.4 percent. What are the current statistics?

Dr. Varmus: It is impossible in any year to determine accurately what percent of NIH research project grants were awarded to white scholars. Questions related to race and gender are optional on all NIH research grant applications as required by federal law. There are a number of applications for which gender and race cannot be determined. Excluding Small Business Innovative Research (SBIR) grants and Small Business Technology Transfer Grants (STTR), of those applicants whose race and/or gender is identified, the data indicates that white scholars received approximately 86 percent of the research project grant awards in fiscal year 1991. In Fiscal Year 1994 the percent distribution of awards by race, including applicants who did not identify their ethnicity are as follows:

Percent Distribution of Competing
Research Project Grant Awards by Race

FY 1994

Asian	Native American	Hispanic	Afro-American	White	Unknown
6.1%	0.2%	1.5%	0.6%	62.4%	29.2%

BREAST CANCER RESEARCH

Mr. Stokes: According to the Congressional Justification, nearly 200,000 new cases of breast cancer will be diagnosed this year, and an estimated 50,000 women will die from the disease. The Committee heard testimony from the Secretary of HHS, the Assistant Secretary for Health, and the Director of the Center for Disease Control emphasizing that the overall death rate for breast cancer in American women declined about 5 percent between 1989 and 1992, the largest short-term decline in four decades. For white women in the 30 to 50 age group, death rates from breast cancer fell 8 to 9 percent over the same time period. However, for African American women, the rate of death due to cancer increased 2.6 percent. To what extent will this information be used to help focus the direction of research?

Dr. Varmus: Breast cancer will strike approximately 183,400 Americans this year and it is estimated that 46,240 women will die from the disease. The 2.6 percent increase in breast cancer mortality since 1989 in African American women relates to African-American women of all ages. Since recent decreases in breast cancer mortality trends for White women over the age of 50 may be due to mammographic screening, it will be imperative that cancer control efforts be directed toward producing a similar effect in African American women, if possible. However, it will also be important to study risk factors in both racial groups in conjunction with mortality trends to try to better understand the differences in breast cancer risk in the two populations which may provide further insight into mortality trends for both races in all age groups. Trends in incidence rates have limited value in this regard because they have been perturbed by early diagnosis due to increases in mammographic screening in both racial groups since the early 1980's. Differences between White and African American women in the natural history of breast tumors have been studied to some degree, but more work will likely need to be done. This latter work may provide some insight into the possible differential impact of screening in the two populations. In general, the continuing increase in breast cancer mortality in African American women identifies a need to better understand the epidemiology of breast cancer in African American women, and to focus cancer control efforts in such a way as to maximize the impact of screening and treatment advances in this group.

A new study tells us that the death rate among African American women is due to factors that can be manipulated; for example, access to high quality care, nutrition changes for a lower fat diet, and increased use of mammography with follow-up on results. These new mortality results for African American women reinforce these earlier conclusions. NCI is working with CDC and other agencies and the State public health agencies and through our information service to achieve these changes.

Mr. Stokes: Last year, researchers discovered the BRCA-1 gene which has been linked to cancer. What are the implications of this finding for accelerating improvements in early detection, treatment and prevention of the disease?

Dr. Varmus: The discovery of the BRCA-1 gene in 1994 holds great promise for the future. This discovery paves the way toward a better understanding of a key contributing factor to this disease. It will soon lead to the development of generic diagnostic tests that will have the power to identify individuals who are at high risk for developing breast and or ovarian cancer in their lifetime. Such diagnostic tests are potentially much more reliable in identifying those at risk than other forms of cancer surveillance now available, thus allowing for more relevant monitoring and more direct provision of preventive interventions to an identified high risk population. In addition to the possibility of much earlier detection and more targeted surveillance of individuals at high risk, this breakthrough allows scientists to focus their efforts in developing better strategies to treat or even prevent the invasive form of breast cancer. Although extremely difficult to predict when such therapies might become available, it was just a few years between the discovery of the gene responsible for cystic fibrosis and a much more targeted approach to treating the underlying cause of this disease through the use of gene therapy.

In spite of this good news about the discovery of BRCA-1, there is still much that needs to be learned. It is likely that there will be a number of other genes that are discovered to cause or be associated with the development of breast cancer. In addition, it is likely that the discovered genes will interact with other genes or with a number of environmental factors that also contribute to the development of this disease. Although a gene-based diagnostic test may be available for families in which cancer is recurring in the coming 1-2 years, it will likely be many more years before such testing will be useful in a more general population. In the meantime, several groups, including the National Advisory Council for Human Genome Research (see attached statement) have suggested that such testing should not become widespread--beyond its research applications--until much more is understood about the meaning of a positive or negative test result, the impact of such testing has on individuals, and the development of recommendations for options and preventive interventions follow.

BREAST CANCER ACTION PLAN

Mr. Stokes: To what extent is the NIH using the Secretary's National Action Plan on Breast Cancer to help direct the research focus of this disease?

Dr. Varmus: Implementation of the National Action Plan on Breast Cancer (NAPBC) is being coordinated by a public/private partnership led by the Deputy Assistant Secretary for Women's Health and the President of the National Breast Cancer Coalition. An overall principle is to involve patients, consumer advocates, industry and Federal agencies in NAPBC activities. With input from the public and private sectors, six priorities were identified for the NAPBC's initial focus:

One priority is to identify strategies to disseminate information about breast cancer and breast health to scientists, consumers, and practitioners using the state-of-the-art technologies available on the information superhighway. Establishing biological resource banks and comprehensive patient data registries to ensure a national resource of information for multiple areas of breast cancer research is another priority. NAPBC participants also identified as a priority ensuring consumer input at all levels in the development of public health and service delivery programs, research studies, and educational efforts.

Additional priorities are to expand the scope and breadth of biomedical and behavioral research activities related to the etiology of breast cancer and to make clinical trials more widely available to women with breast cancer and women who are at risk for breast cancer by decreasing barriers to participation. A final priority is to implement a comprehensive plan to address the needs of individuals carrying breast cancer susceptibility genes and recommend educational interventions for consumers, health care providers, and at-risk patient groups.

NCI is working closely with the Steering Committee of the NAPBC to support these priorities, including participating in NAPBC efforts to develop initiatives that address the priorities. NCI and the PHS Office on Women's Health co-sponsored a conference on Breast Cancer Resources to Facilitate Research to review existing resources for biological materials related to breast cancer research and to discuss issues of informed consent, confidentiality, and access to materials. NCI supports a Cooperative Breast Cancer Tissue Registry that is a resource to investigators who need specimens to validate promising prognostic markers. There are plans to expand this registry to include more tissue specimens and data from minority populations. NCI's Breast Cancer Prevention Trial is trying different strategies to increase participation of minority populations. NCI is working with other NIH Institutes and Federal agencies to develop a coordinated approach to issues related to genetic screening for breast cancer. This includes coordinating efforts with NAPBC participants as a research agenda is framed.

The NAPBC Steering Committee is considering the NIH peer review process and funding mechanisms as possible models for supporting breast cancer research through the National Action Plan.

NCI's FY 1995 appropriation included $10 million to begin implementing the NAPBC. The President's Budget for NCI in FY 1996 requests a total of $20 million for support of the NAPBC.

BREAST CANCER FUNDING

Mr. Stokes: How much is included in the FY 1996 budget request for breast cancer?

Dr. Varmus: The amount included in the FY 1996 budget is $426.2 million.

Mr. Stokes: How does this compare with the funding level for FY 1995?

Dr. Varmus: The FY 1996 estimate of $426.2 million is an increase of 13 percent over the FY 1995 estimate of $377.1 million.

Mr. Stokes: How does this compare with the funding level for FY 1994?

Dr. Varmus: The NIH spent $306.1 million in breast cancer research in FY 1994. The FY 1996 estimate of $426.1 million projects a 39 percent increase over 1994.

PREVALENCE RATES FOR PROSTATE CANCER

Mr. Stokes: According to the Congressional Justification, prostate cancer is the most commonly diagnosed cancer among men in the United States. In testimony before the Committee last year, the Director of NCI emphasized that African American males have the highest rate of prostate cancer than any other segment of the world's population. What has been the prevalence of this disease in the last five to ten year period?

Dr. Varmus: Estimates of the prevalence of cancer have been developed using data for the State of Connecticut. This has been possible because of the existence of a population-based cancer registry in the state since 1940 with data going back to 1935. The estimate of the prevalence of prostate cancer for all males in the state for the year 1990 was 434.1 per 100,000 (adjusted to the 1970 Standard Population). A "prevalent case" is defined as a person who was alive on January 1, 1990 with a previous diagnosis of invasive prostate cancer sometime between January 1, 1935 and December 31, 1989. They were also a resident of the state at the time of their diagnosis of prostate cancer. Applying age-specific prevalence rates for Connecticut to the US population in 1990 indicated that there were 551,656 prevalent prostate cancer cases at that time. Rates are not available by race.

Another often used measure of cancer is incidence, the number of new cases diagnosed in a time period. The incidence of prostate cancer has been rising rapidly, due largely, though not completely, to the use of early detection techniques such as transurethral resection of the prostate (TURP) and prostate specific antigen (PSA). In 1994, there were an estimated 200,000 new cases, while in 1995 there will be an estimated 244,000 new cases.

PROSTATE CANCER FUNDING

Mr. Stokes: Is research on prostate cancer limited to the Cancer Institute?

Dr. Varmus: In addition to the Cancer Institute, prostate cancer research is supported by the Institutes of Diabetes and Digestive and Kidney Diseases, Environmental Health Sciences, Aging, Nursing, and the Centers for Research Resources and Human Genome Research.

Mr. Stokes: To what extent is research on this disease considered to be a trans NIH initiative?

Dr. Varmus: Prostate cancer is a trans-NIH disease area. It is funded by six other Institutes and Centers at the National Institutes of Health.

Mr. Stokes: According to the Justification, scientists have recently discovered a genetic defect in prostate tumors that results in the inactivation of an enzyme needed to protect normal cells from environmental carcinogens. It further states that further research to elucidate how this critical enzyme is regulated may lead to new diagnostic or treatment measures for prostrate cancer. How much is included in the FY 1996 Budget request for prostate cancer?

Dr. Varmus: The FY 1996 budget estimate for prostate cancer is $79.8 million.

Mr. Stokes: How does this compare with the funding level for FY 1995?

Dr. Varmus: The FY 1996 budget includes a three percent increase over the FY 1995 level of $77.6 million.

Mr. Stokes: How does this compare with the funding level for FY 1994?

Dr. Varmus: In FY 1994 the NIH spent $69.2 million on this disease. The FY 1996 estimate is an increase of $10.6 million or 15 percent.

PROSTATE CANCER RESEARCH PROGRAMS

Mr. Stokes: Would you bring the Committee up-to-date on the major NIH activities that are underway with respect to prostate cancer?

Dr. Varmus: The NIH supports a broad-based portfolio of basic and clinical investigation of all aspects of prostate cancer from prevention to detection to treatment to address fundamental issues in cancer etiology, epidemiology, tumor biology, vaccine development, prevention, early detection and diagnosis, and treatment. The National Cancer Institute (NCI), as the lead NIH institute, cooperates with other sister institutes and agencies of government. For example, NCI contributes to the National Institute of Diabetes and Digestive and Kidney Disease's (NIDDK) Urology Research Program through the O'Brien Research Centers. The National Institute of Environmental Health Sciences (NIEHS) and the Environmental Protection Agency (EPA) are active collaborators in NCI's pivotal Agriculture Health Study, in which prostate cancer is a major focus. The Veterans Administration and the NCI Clinical Cooperative Groups collaborate in the Prostate Intervention versus Observation Trial (PIVOT), to determine the role of aggressive surgical intervention in the management and survival of men with early-stage prostate cancer. The oncology communities of the NCI cancer centers are intensifying research portfolios to address prostate cancer and to change the impact that prostate cancer presently has on the duration, productivity and quality of life for all men affected by this disease.

RATES AMONG AFRICAN AMERICANS

The increase in prostate cancer mortality over the last 20 years in African American men is almost twice that of white Americans and is an area of intense investigation. Recent epidemiologic studies have demonstrated that the excess mortality of African-American men in the Southeastern United States relative to African-American men in other parts of the country may be linked to employment in farming. Studies comparing African-Americans and white Americans demonstrate that both groups have similar age-specific baseline serum levels of Prostate Specific Antigen (PSA) and similar familial risks. The large-scale Agriculture Health Study, the Migrant Farm Workers Study, the Triana Study--in conjunction with the Tennessee Valley Authority--and the epidemiologic studies of the Prostate Cancer Prevention Trial (PCPT) will shed light on these issues. The prostate cancer SPOREs are examining the differential expressions of certain genes and serological biomarkers in the context of racial/ethnic differences. NCI has recently issued two Requests for Application (RFAs) for funding within the next 6-12 months--"The Molecular Epidemiology of Prostate Cancer" and "Prostate Cancer Programs within Cancer Centers"--to stimulate clinical investigations in this research area. In addition, NCI proposes to develop an RFA, "Prediction of Prostate Cancer in African American Men," to focus on the identification of biomarkers and biological parameters as predictors of prostate cancer risk and tumor biology in this population.

TUMOR GENETICS AND BIOLOGY

Prostate cancer genetic studies show similarities between the inheritance of prostate cancer and the inheritance of breast cancer. Investigators are rapidly closing in on potential "prostate cancer genes." Provocatively, some cases of familial prostate cancer may be linked to the "breast cancer-1" (BRCA-1) gene. A recent finding from the Johns Hopkins Prostate Specialized Program of Research Excellence (SPORE) is that a gene (GSTP-1) responsible for detoxifying potential carcinogens is consistently altered in cancerous prostatic cells, but not in noncancerous cells, such that its expression is suppressed. This discovery may serve as a tool for early detection, risk identification and monitoring of the effects of a therapeutic or prevention intervention. Developing agents to reverse the GSTP-1 alterations could yield a targeted chemoprevention strategy.

Research in prostate cancer tumor biology continues to be enhanced by the Cooperative Network for Molecular Genetic and Cytogenetic Markers for Prostate Cancer, a network of six research groups. The dissection of components such as angiogenesis, mutations in the androgen receptors, interactive molecules responsible for intercellular communications and adhesion, and proteins that comprise the structural scaffold within the nucleus (the nuclear matrix) are leading to ways to define the cell properties conferring malignant behavior and to discriminate nonmalignant from malignant cells. Each of these components is a ripe target for therapy and for the prevention of critical transforming events, for instance, metastasis. The development of innovative animal models of prostate cancer are important to the study of prostate cancer biology, prevention and therapy. The transgenic mouse prostate reconstitution (MPR) model, developed by scientists at the NCI supported Matsunaga-Conte SPORE at Baylor University, and other novel xenograft models of human prostate cancer cell lines are providing fertile testing grounds.

VACCINE RESEARCH

Novel vaccine candidates that target prostate cancer are now entering clinical testing. Mutations in the ras oncogene and overexpression of the encoded Ras proteins are often found in prostate cancer, and scientists are beginning to test vaccine constructs that use these abnormal proteins and peptides. The PSA protein is a potential immunological target: PSA peptides and a vaccine linking the gene for PSA with the highly immunogenic recombinant vaccinia vector will enter clinical testing soon. Scientists are embarking on a gene therapy-based vaccine that will be tested in an adjuvant setting in men with Stage C prostate cancer.

PREVENTION RESEARCH

The Prostate Cancer Prevention Trial (PCPT) tests the role of finasteride (Proscar), as a potential preventive agent. This study, is being conducted through the Clinical Cooperative Groups, 223 participating institutions. The PCPT is accruing men over age 54 and with PSA less than 3 ug/l; more than 22,000 men have been enrolled and about 14,000 men are currently on study (the target is 18,000 men). To date, roughly 7.5 percent of the study population are minorities--4 percent African-American and 3.5 percent Hispanic. In addition the PCPT has established a serum and tissue bank for serially-obtained clinical samples that will provide fundamental data regarding normal and malignant prostate biology, genetic and environmental/occupational epidemiology, screening/early detection (measuring the impact of finasteride on serum PSA levels), and any finasteride-induced changes in lipid metabolism. Since approximately 1 million men in the United States are taking finasteride for therapy of benign prostatic hypertrophy, the study will expand several facets of knowledge regarding this widely-used drug and, in this way, stands to serve diverse aspects of men's health.

SCREENING RESEARCH

The Prostate, Lung Colon and Ovary (PLCO) trial, underway at 10 institutions across the nation, seeks to determine the value of routine cancer screening by comparing intensive yearly screening for 4 years with routine medical care in 74,000 men and 74,000 women ages 60-74. Screening modalities for prostate cancer include digital rectal examination and serum PSA determination, and transrectal ultrasound if indicated. A 2-year pilot phase, accruing 14,000 participants, was completed in September 1994 and is being analyzed to determine any need for changes in study design, with special attention to whether or not certain screening modalities are already being performed routinely in the control group.

CANCER INFORMATION

A prostate cancer educational campaign focuses on early detection and treatment and targets older men, especially African Americans. NCI's International Cancer Information Center (ICIC) is responsible for information dissemination through scientific publications and databases. Its treatment database, Physician's Data Query (PDQ), provides data on state-of-the-art treatment for all major cancers; a geographically matrixed file of active research protocols enabling physicians to identify clinical trials appropriate for their cancer patients; an archival file of closed protocols; and a geographically organized directory of physicians and organizations providing cancer care.

CLINICAL TRIAL PARTICIPATION

Clinical investigation of prostate cancer remains a high priority, with involvement of intramural and extramural scientists, including NCI's Clinical Cooperative Groups. To this end, NCI's Cancer Drug Screen now incorporates two human prostate cancer cell lines in its human tumor cell screening panel--with four additional lines under development--and has identified 150 compounds with degrees of selective activity against prostate cancer that are now undergoing targeted preclinical development. A key clinical study, mentioned above, is the VA/NCI Intergroup PIVOT study which compares aggressive surgical intervention with clinical observation in early stage prostate cancer. A similar Cooperative Group study, beginning in 1995, is addressing the role of radiation therapy in the management of early stage prostate cancer, the Radiation Intervention versus Observation Trial (RIVOT). The NCI Cooperative Groups are planning to implement 12 new Phase III trials of hormonal and cytotoxic agents in all stages of prostate cancer. In addition, there are major clinical programs at the NIH Clinical Center and across the nation to test new modalities: heavy particle and multi-dimensional radiation therapies, anti-angiogenesis strategies, inhibition of intracellular signalling pathways, enhancement of programmed cell death, differentiation therapies such as retinoids, and monoclonal antibody-based strategies such as immunotoxins. This broad and expanding portfolio of clinical exploration is the outgrowth of our understanding of cell and tissue biology on its most basic developmental levels and as it applies to the prostate.

SUMMARY

In sum, this response provides a brief synopsis of NIH's cross-cutting basic and clinical investigations targeting prostate cancer research. There is a steep learning curve that, in turn, is generating excitement and progress in each area of investigation. And clearly, there is also a great distance to go before we accomplish the goal of disease eradication for the large numbers of men who stand to benefit from these efforts.

Mr. Stokes: As there appears to be no consensus on the appropriate treatment for prostate cancer, to what extent would a joint NIH-CDC consensus conference on this disease and the development of a national plan be useful in helping to direct and focus basic, applied, clinical and epidemiological research?

Dr. Varmus: At the present time, there is no consensus regarding many aspects of the management of prostate cancer, from screening and early detection to treatment at the various stages of disease and the possibility of prevention. In June 1987, the National Cancer Institute (NCI) held a Consensus Development Conference on the "Management of Clinically Localized Prostate Cancer." The conclusions reached at that time, and published in a 1988 Journal of the National Cancer Institute Monograph (Monograph #7), were that radical prostatectomy surgery, radiation therapy and conservative management, observation, could be used to manage early-stage prostate cancer, but the relative merits of each alone or in combination were unknown. Along these lines, the American Urological Association (AUA) recently commissioned a literature review of the scientific data available on the therapy of early stage prostate cancer. The review panel included several NCI-supported scientists. This comprehensive review again failed to disclose a clear answer regarding the appropriate roles of surgery, radiation and/or clinical observation--a conclusion that is not different from NCI Consensus Development Conference in June 1987--and supported the need for NCI's large-scale, randomized clinical trials, PIVOT and RIVOT, to define the roles of each modality in the optimal management of early-stage prostate cancer.

CLINICAL TRIALS

To this end, the National Cancer Institute is conducting three large-scale, randomized, controlled clinical trials that will shed great light on the optimal management of prostate cancer: 1) PIVOT (Prostate Intervention versus Observation Trial--a collaborative effort between the Veterans's Administration and the NCI Clinical Cooperative Groups Intergroup--to determine the role of aggressive surgical intervention (radical prostatectomy) vs. observation and conservative management in early-stage (clinically localized) prostate cancer in 2,000 men; 2) PLCO (Prostate, Lung, Colon and Ovary) trial to determine the impact of routine PSA screening on early detection and survival of prostate cancer (and will also evaluate appropriate screening for colon and lung cancers) in 74,000 men ages 60-74; and 3) PCPT (Prostate Cancer Prevention Trial), evaluating the potential for the 5-alpha-reductase inhibitor finasteride (Proscar) to prevent prostate cancer in 18,000 men over age 54. A new large-scale, randomized trial being conducted by the NCI Intergroup beginning in 1995--RIVOT (Radiation Intervention versus Observation Trial)--is similar in design to the PIVOT trial and will evaluate the role of early radiation vs. observation and conservative management in 2,000 men with early-stage disease. The results of these trials, as they become available individually and collectively, will form the basis for a Consensus Development Conference at a time when such a conference can be most informative.

PSA

There is an ongoing legitimate controversy regarding the efficacy of prostate cancer screening with the modalities presently at hand. Since 1988, there have been at least a dozen groups of experts from the United States, Canada and Europe who have scrutinized the value of serum PSA levels as a potential tool for the screening and early detection of asymptomatic, subclinical prostate cancer. While two of these groups felt that PSA-based screening should be conducted as part of standard medical practice, the other 10 groups, following extensive review of the available scientific data, concluded that the issue of PSA screening required an in-depth, well-controlled, large-scale clinical trial. Based on this controversy, NCI, with the expert advice from scientists at NIDDK, has developed and implemented the PLCO trial and the laboratory correlative studies within the framework of the PCPT. Further, in November 1993, the AUA in conjunction with NCI, the Centers for Disease Control and Prevention (CDCP) and the American Cancer Society (ACS) held a conference to address the current state of knowledge regarding prostate cancer screening. As a result of this conference, the AUA has endorsed the need for NCI's PLCO trial in order to place PSA-based screening in its proper context with regard to the overall management of prostate cancer, particularly in elderly men.

COOPERATIVE RESEARCH

With regard to a national plan for prostate cancer research, the NIH supports a broad-based and comprehensive portfolio of intramural and extramural investigations that cover all research disciplines. The prostate cancer research agenda is informed by ongoing collaborations among NCI and the categorical NIH institutes, in particular NIDDK, National Institute of Environmental Health Sciences (NIEHS) and National Center of Human Genome Research (NCHGR), as well as close interactions with the AUA, ACS and CDC. The Agriculture Health Study--the nation's largest-ever epidemiologic study of 100,000 farmers and their families--is a collaboration effort among the NCI, NIEHS and the EPA to identify and assess factors that may relate to the detected excesses of certain cancers, including prostate cancer, among farmers. The demographic characteristics and identification of possible risk factors for prostate cancer are one major focus of this study. NCI and NIDDK are jointly sponsoring an upcoming Working Session on Prostate Cancer Prevention. Further, NIDDK scientists serve on NCI's advisory board for the development, implementation and evaluation of both the PLCO and PCPT trials. Interagency collaborations are also exemplified by the joint development of workshops and conferences such as: 1) 1993 Workshops on the Early Detection of Prostate Cancer--one co-sponsored by NCI, CDC, ACHPR and the Navy Bureau of Medicine and Surgery and one co-sponsored by NCI, AUA and ACS; 2) 1993 Conference on Vasectomy and Prostate Cancer (NCI, NIDDK, NICHD); 3) 1994 Conference on Metal Ions in Biology and Medicine (NCI, Food and Drug Administration); and 4) Workshop on Dietary Phytoestrogens (NCI, NIEHS). The workshops and conferences define and evaluate the state of knowledge (and lack thereof) regarding the specific subject area, serve as cornerstones for identifying existing and emerging scientific opportunities, and form the basis for the development of Program Announcements and Requests for Applications for innovative research addressing such areas of scientific opportunity. The NCI also benefits from the input and active involvement of the advocacy group "Us Too" in the PCPT; members of "Us Too" are helping to recruit brothers of prostate cancer patients, as members of a potentially high risk subgroup, for possible entry into the PCPT.

RE-EMERGING INFECTIOUS DISEASES

Mr. Stokes: The re-emergence of infectious diseases is causing tremendous national concern. What are the most significant diseases that fall into this category, and what research is underway to address them?

Dr. Varmus: Recent media attention has highlighted the potential for emerging viral diseases, but in fact the possibility also exits for many bacterial, fungal or parasitic infections to emerge or re-emerge in the U.S. The 1992 Institute of Medicine report on Emerging Infections: Microbial Threats to Health in the United States, presented a lengthy list of emergent diseases in each of these categories. Moreover, we are all aware of recent examples such as unexpected outbreaks of hantavirus infection in the Southwest, Lyme Disease in the Northeast, coccidioidomycosis in California and cryptosporidiosis in Wisconsin. Increases in population density, urbanization, and worldwide commerce and travel, as well as environmental changes, all contribute to the prospects for emergence or re-emergence of infectious diseases. In addition, indiscriminant use of antimicrobials has led to the development of drug resistance by some pathogens that were once thought to be controllable, such as tuberculosis and malaria.

NIAID has made a concerted effort to address emerging disease threats as they appear, for example, by greatly expanding research efforts on diseases such as AIDS, Lyme and tuberculosis. The exact nature of any future emerging disease threat may be difficult to predict, however. To successfully confront this challenge requires critical knowledge of the fundamental biology of infectious agents and the clinical disease processes they induce. For that reason, NIAID supports a broad and comprehensive program of fundamental research, research training and applied research to strengthen national surveillance and response capabilities. Topics related to emerging diseases include research on: 1) fundamental aspects of microbial physiology, genetics and biochemistry that will elucidate the mechanisms of antibiotic resistance and facilitate identification of new intervention strategies; 2) pathogenesis of viral, bacterial, fungal and parasitic diseases; 3) host immune responses to infection; 4) the development of new interventions, including vaccines, therapeutics and diagnostic tests; and, 5) transmission dynamics of infectious diseases, including studies of vector biology and environmental influences. Since it is clear that the issue of emerging diseases is global in scope and cannot be addressed by our country in isolation, the NIAID also maintains strong international ties through programs such as the International Collaborations in Infectious Diseases Research.

Mr. Stokes: In your professional judgement, what type of national strategy is needed and would be effective in addressing this national problem?

Dr. Varmus: The problem presented by the threat of emerging infectious diseases requires that our country maintain its international leadership role in basic biomedical epidemiologic research. Laboratory and epidemiologic research are the essential twin foundations upon which sound surveillance and appropriate response are based, and this is especially true in regard to emerging infections. Epidemiologic research into transmission patterns and risk factors provide the critical link between a disease and its causative agent that allows an effective public health response. No effective control measure may yet be available, however, for newly emerging diseases or for those that are re-emerging due to the development of resistance to previous control methods. Our ability to address such threats adequately will in large part depend on the success of basic biomedical research. Research to improve fundamental understanding of the processes of microbial evolution, the genetic basis for virulence, and the immune mechanisms involved in resistance and disease lays the groundwork for development of new or improved diagnostic and therapeutic strategies, vaccines, and methods to prevent the transmission of infectious agents. Efforts to protect our country from emerging disease threats will also require sustained support for international research and training. It is intuitively obvious that an improved capacity to detect and contain infectious disease threats where they originate, before they spread internationally, will benefit the U.S. With ever increasing international travel and commerce, this country cannot afford a "fortress mentality". Importation of new microbes can occur with every international air flight, and every shipment of food or other goods. Support for the further development of strong public health capabilities abroad, particularly in tropical and other developing regions where infectious diseases often tend to first emerge, is a national security issue. Long-term, sustainable, support for collaborative international laboratory and epidemiologic research and research training programs provides an important opportunity to achieve this goal.

DIAGNOSTIC TESTING FOR TUBERCULOSIS

Mr. Stokes: What is the status of the rapid diagnostic test for Tuberculosis?

Dr. Varmus: There are two new tests that can be used for the rapid diagnosis of tuberculosis:

1) The Polymerase Chain Reaction (PCR) for the early detection of M. tb in clinical samples is a test system that is under active development by three manufactures--Hoffman LaRoche, GeneProbe, and Becton & Dickenson. Although some problems remain regarding the sensitivity and specificity of these diagnostic kits, it is anticipated that the technology exists to overcome these problems.

2) The Luciferase assay for drug susceptibility test shows great promise. Although still under development, most of the technical problems have been resolved. Under an NIAID contract to Case Western Reserve University, the test system is currently being evaluated at Monteifore Hospital Medical Center in New York City. Preliminary data has shown the specificity to be excellent. Efforts are now directed to improving the sensitivity of the test. The luciferase has been licensed to Becton & Dickenson for product development, although this company has recently decided not to pursue this opportunity.

ORMH PILOT PROJECTS

Mr. Stokes: To what extent have Office of Research on Minority Health (ORMH) pilot projects that have proven to be successful been fully adopted for support by the Institutes, Centers and Divisions of the NIH?

Dr. Varmus: Two types of collaborations occur between the ORMH and the Institutes, Centers, and Divisions (ICDs). The more common scenario is that funds appropriated to the Minority Health Initiative (MHI) are used to support new minority health research programs during their pilot stages. However, in some cases, ORMH/MHI funds are leveraged through equal cost-sharing with the partner ICD from the outset. Notably, the National Institute of Diabetes and Digestive and Kidney Diseases has been a full partner with the ORMH, bearing an equal share of the cost of new joint programs, including several research projects focusing on diabetes prevention in minority populations.

Because many of the research projects supported through the MHI are long-term in nature, and the initiative is only in its third fiscal year, there has been insufficient time to reach definitive conclusions about the success of these programs. However, the ORMH has developed a transition plan whereby ORMH/MHI funding of projects deemed successful will be phased out over a 2-year period and financial responsibility for the projects' continuation will be transferred to the relevant ICD. The ICDs are fully aware of their responsibilities under this transition plan.

The ORMH is currently in the process of implementing a comprehensive prospective evaluation system that will assess the effectiveness of all NIH minority research and training programs. The evaluation system will be fully implemented by the end of FY 1996. At that time, ORMH will have the necessary information to determine program effectiveness. Programs deemed ineffective will be phased out, while those that have demonstrated success will be transferred to the ICDs under the terms of the transition plan.

ORMH FACT FINDING REPORT

Mr. Stokes: Last year, the Office indicated that it would be updating its original fact finding report. What is the status of the addendum?

Dr. Varmus: As a followup to the 1991 consultative effort that resulted in the Fact-Finding Team (FFT) report, the ORMH convened the National Conference on Minority Health Research and Research Training in Chicago, Illinois, on March 27-30, 1994. The draft report of that conference, which includes new recommendations from the minority community and which are intended to provide guidance on the direction of ORMH programs for the period 1995-2000, which will be submitted to the Committee. The following is an abstract of the report:

The consensus of the participants, as expressed in their responses to a Conference evaluation questionnaire, was (1) that ORMH personnel have been receptive to input from the community; (2) that the ORMH has made good progress in generating programs responsive to the original 13 FFT recommendations for minority health research and training; and (3) that the ORMH has increased awareness of minority concerns at all levels of the NIH. The participants agreed that the ORMH should continue to encourage NIH Institutes, Centers and Divisions (ICDs) to fund more minority research and to collaborate with other government agencies to leverage funds dedicated to minority programs. Over three-quarters of the Conference participants felt that the ORMH is achieving its dual goals of increasing research on diseases affecting minority groups and involving more minorities in biomedical research.

The report summarizes the Conference proceedings and presents recommendations based on the discussions and views expressed during the meeting. The community expressed strong support for the continued pursuit of the original 13 FFT recommendations. It recommended additional efforts in the areas of behavioral and social science research, infrastructure development, data collection and dissemination, community outreach, and collaboration with governmental and nongovernmental entities. The community emphasized that the ORMH should function as a strong trans-NIH office with responsibility for the coordination and review of all NIH minority health and training programs. To assist the ORMH in the development of its programmatic initiatives, the community recommended the formation of an external Advisory Committee.

FUNDING FOR CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and has yielded comparable economic savings. What level of funding is included in the FY 1996 Budget for Clinical Trials?

Dr. Varmus: The FY 1996 budget includes $1,201 million for research involving clinical trials.

Mr. Stokes: How many trials would be funded?

Dr. Varmus: The number of clinical trials that would be funded totals 1,953.

Mr. Stokes: How many of these trials are new and how many are ongoing?

Dr. Varmus: Of these 1,550 would be ongoing and 403 would be new.

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously?

Dr. Varmus: A number of important clinical trials supported by the NIH received widespread attention in the medical literature and in the mass media this fiscal year. These include studies showing that: surgery can prevent stroke in carefully selected individuals with severe narrowing of a major artery in the neck; a new drug-releasing device can treat a severe eye disease that causes blindness in AIDS patients; a new pertussis vaccine can prevent whooping cough in infants; estrogen replacement can improve the risk factors for heart disease in older women; eye surgery for a certain potentially blinding condition is ineffective and may be harmful to patients' vision; treatment with the drug minocycline is safe and reduces joint pain and swelling in patients with arthritis; the drug hydroxyurea reduces the painful and life-threatening complications of sickle cell disease; and the transmission of HIV from infected pregnant women to their newborn offspring can be markedly reduced by giving women the drug AZT. The results of all of these studies were expeditiously conveyed to researchers, health care professionals, patients and the general public in a number of ways including through medical journal publication and online databases and through press releases and press conferences when appropriate to stimulate news media coverage. In some instances, NIH takes additional steps to convey important clinical trial information through conferences for health care providers or health education campaigns aimed at patients and their physicians. For example, following a 10-year clinical trial showing that intensive control of blood sugar levels can significantly reduce the serious side effects of insulin-dependent diabetes, the NIDDK has launched an outreach program promoting the message "Do Your Level Best" through which health care professionals and patients receive an information kit on improving blood sugar control. Approximately 20 million people were reached during November 1994, and more than 35,000 copies of the information kit have been distributed.

Mr. Stokes: Is there a specific system in place for disseminating such information, explain.

Dr. Varmus: Each clinical trial differs according to the disease of its focus, the strength of its findings, and in other ways such as whether it is a treatment or prevention study. For this reason, the information dissemination plan for each clinical trial is individually designed. However, NIH has set guidelines, published in the Journal of the American Medical Association in June 1993, for alerting physicians and the public about clinical trial findings in cases in which timely and broad dissemination could prevent morbidity and mortality. The guidelines reflect the NIH's legislated responsibility and ethical obligation to issue such clinical alerts. The guidelines spell out the roles of the Institute Directors and the data safety and monitoring committees that are a part of many clinical trials. They also spell out the agreements NIH has made with medical journal editors to speed both public announcement and journal publication and describe the special efforts to notify patients participating in the trials, the medical community, and the news media.

ASSESSMENT OF ADMINISTRATION OF AIDS FUNDING

Mr. Stokes: In response to the provisions contained in the Revitalization Act of 1993, the FY 1996 Budget continues to include all AIDS and related funds in a single appropriation account for the Office of AIDS Research. In your professional judgement, how well is this approach working?

Dr. Varmus: The Congressional appropriation was less than the President's request in FY 1995; hence the single appropriation process allowed the OAR to determine the appropriate shift in funds to ICDs, based on scientific opportunities set forth in the comprehensive plan.

Under the new system, the single appropriation allows the OAR to preserve the highest priority scientific areas, determined by the consensus recommendations of the plan.

The single appropriation allows the Director of OAR to bring about the redirection of research across all of the institutes and allows more efficient management and scientific oversight of the vast HIV/AIDS research effort at the NIH.

Thus, the single appropriation is essential for better management and scientific oversight of the vast HIV/AIDS research effort at the NIH, particularly in a time of fiscal constraint.

Mr. Stokes: Are there specific concerns with regard to this approach?

Dr. Varmus: Initially, some of the Institutes and Centers of the NIH were concerned that a single appropriation to the Office of AIDS Research (OAR) could hamper their ability to execute planned Requests for Applications in a timely manner as well as impact on other aspects of research portfolio management. It is clear to the Institutes and Centers now that the OAR keeps them informed at every level of the budget development process so that their plans can be adjusted in a timely manner. We believe most concerns have been resolved and this process appears to have worked well for both the NIH and the Appropriations Committee.

EFFECTS OF FY 1995 PROPOSED RESCISSION

Mr. Stokes: The recently reported House Bill includes approximately $1.7 billion in cuts and program terminations within the Department of Health and Human Services. This figure includes $70 million in rescinded funds for NIH. The $20 million in funding cuts for extramural facilities eliminates that program. There is also a $50 million rescission for prior year construction funds. What is the effect of these reductions?

Dr. Varmus: The impact of the rescission of $20 million in Extramural Construction funds will be the loss of the entire program for at least this year.

In FY 1994, the NCRR received 68 applications requesting approximately $79 million in construction funds. Because of the matching requirement of the program this actually represents at least $160 million in construction projects. The NCRR funded eight projects for a total of about $7 million in FY 1994. Applications for the FY 1995 program were requested in December of 1994; applications are due March 9, 1995. To date 117 letters-of-intent to apply have been received, representing institutions in 36 states, the District of Columbia, and Puerto Rico. Awards are scheduled to be made in September, 1995.

The rescission of $50 million in the Buildings and Facilities appropriation will be taken from funds originally appropriated for Phase II of the William H. Natcher Building.

NIH had already determined not to construct Phase II of this building. Funds were to be redirected in order to address critical physical and functional deficiencies within the Clinical Center Complex and several of the older research buildings on campus. These deficiencies have been confirmed by an independent review by the U.S. Army Corps of Engineers.

For the Clinical Center, an interim program is underway to extend the service life of the facility 12 to 15 years. The rescission will jeopardize the NIH's ability to complete the Clinical Center within the window of opportunity available to sustain the clinical research program.

ELIMINATION OF OFFICE ON BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

Mr. Stokes: In testimony before the Subcommittee, the Heritage Foundation recommended the elimination of the Office of Behavioral and Social Sciences Research. Is this program's mission no longer viable, explain.

Dr. Varmus: In accord with Section 203 of the NIH Revitalization Act of 1993 (Public Law 103-43), the National Institutes of Health (NIH) organized this Office to provide a focal point for the coordination of NIH-wide activities related to behavioral and social science research. The Office was established within the Office of the Director, NIH, in July 1994. Following a nationwide search for an Associate Director for Behavioral and Social Sciences Research, the NIH Director has selected a candidate for this position. The NIH has moved expeditiously to fill this vacancy and is currently awaiting official appointment of the nominee by the Assistant Secretary for Health. When confirmed, that individual will assume full responsibility for the direction of the Office.

IMPROVING SICKLE CELL THERAPIES

Mr. Stokes: As disease prevention, early detection, and treatment, collaboration between the Centers for Disease Control, the National Institutes of Health, and the Food and Drug Administration has proven to result in the accelerated application of advances stemming from biomedical research. To what extent will a similar collaborative approach be used to advance the recent development of the sickle cell therapy to improve the quality of life for those suffering from this disease?

Dr. Varmus: The recent advances of hydroxyurea therapy are extremely promising for selected adult patients with sickle cell anemia. The opportunity to maximize this therapeutic approach will require close collaboration with the Food and Drug Administration (FDA) for a number of reasons. First of all, hydroxyurea is not approved for use in sickle cell disease, and it will be critical for the FDA to work with the manufacturer to evaluate the data from the Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia for "on-label" use. In addition, there is increasing interest in using this drug in pediatric patients. The Institute recently began a pediatric study of hydroxyurea at four of the Comprehensive Sickle Cell Centers. Collaboration with the FDA to evaluate this pediatric data is essential to the expanded use of hydroxyurea in children. The Centers for Disease Control (CDC) could be invaluable in disseminating the results of this clinical trial through their programs on minority health.

Mr. Stokes: What additional research is underway to further this advancement in the treatment of the Sickle Cell Disease?

Dr. Varmus: Although the recent therapeutic advance is a giant step forward, the Institute continues to pursue parallel efforts in other areas of research directed at improving the treatment of patients with sickle cell disease. We recognize that hydroxyurea is not the drug of choice for all patients and the NHLBI supports research on other agents that increase fetal hemoglobin. One such group of non-cytotoxic agents, butyrate salts, are under investigation. The hematopoietic growth factor, erythropoietin, also increases fetal hemoglobin and preliminary studies of hydroxyurea and erythropoietin indicate that there is a synergistic effect with these two agents. Other approaches examine mechanisms that effect water and ion transport. A small number of selected patients have been treated successfully with allogeneic bone marrow transplantation and ongoing research is designed to further decrease the risks of this therapeutic option.

NUTRITION RESEARCH

Mr. Stokes: To what extent has the agency intensified its research on the role of nutrition in health?

Dr. Varmus: The NIH has taken a variety of steps to intensify research on the role of nutrition in health, including issuing research solicitations and supporting conferences on nutrition research. In FY 1994, for example, the NIH focussed on applying the concepts and techniques of molecular biology to nutrition research through a trans-NIH RFA, entitled "Nutrient Modulation of Cell Integrity and Repair Mechanisms." Eleven of the NIH Institutes and the Office of Research on Minority Health supported the RFA, which will fund $4-5 million of bionutrition research. The responses were reviewed earlier this month. Many of them have been judged to be outstanding and to offer creative new approaches. This type of trans-NIH cooperation helps nutrition research in several ways. This availability of a substantial commitment of funds attracts researchers from different fields; the focus of the RFA encourages new approaches and methodologies; and the simulataneous participation of many of the Institutes maximizes the efficiency of the application process for researchers, reviewers, and NIH staff. In addition, virtually all of the NIH Institutes have a significant and increasing investment in overall nutrition research and training. The FY 1996 budget contains an estimate of $410 million for nutrition, an increase of 3% over the FY 1995 Estimate of $398 million.

HEALTH IMPLICATION OF FY 1996 PROPOSED BUDGET CUTS

Mr. Stokes: While not under the purview of the NIH, as proposals to cut food stamps, school lunches, and other nutrition programs are intensifying, whether the funding cuts are identified as caps, level funding, or slowing the growth, if implemented, what could be the health and related implications of such actions in the short and long-term?

Dr. Varmus: As health care costs continue to escalate, the role of nutrition becomes increasingly important, since it costs less to prevent disease than to treat it. The major causes of morbidity and mortality in our population--cancer, cardiovascular diseases, renal diseases and hypertension--are all strongly affected by nutrition. Proper nutrition is essential for our children to grow into healthy adults and is critical in prenatal care. School lunches often provide the sole source of nutrients fundamental for healthy growth and development in school age children and adolescents. The importance of diet cannot be overemphasized in the prevention of chronic disease and in influencing the course of disease, especially in the critically ill. Malnutrition among the elderly, which is already increasing at an alarming rate, stands to grow exponentially without the support of nutrition programs. It would appear that adequate nutrition is both cost effective in the short and long term and benefits every American. Proposals that would adversely affect nutrition programs could thus have a very negative impact on the nation's health.

NEUROLOGICAL RESEARCH INVESTMENT

Mr. Stokes: Last month, the Committee had the opportunity to hear testimony from the nation's Nobel Laureates. We welcomed the insight they provided on the status of the nation's biomedical research enterprise. They indicated the neurological research was one of the most important areas that, if enhanced, offered considerable opportunity to further medical advances. What makes this area of research a prime investment at this time?

Dr. Varmus: The brain is the source of those qualities that make us most human-- thought, language and feeling, and is the most complicated organ in the body. Its diseases are debilitating, expensive and difficult to treat. Previous progress in neurological research has been hampered by the anatomical, molecular and functional complexity of the brain, by its inaccessibility to drugs that do not pass the blood-brain barrier, and by the inability of mature nerve cells in the brain to regenerate following injury. Now the remarkable development of new tools and new knowledge allow us for the first time to address major questions of brain function and to devise therapies that will prevent or correct the effects of disease and injury. These advances open new frontiers for research into neurological disease and put neuroscience research at the forefront of biomedical science today.

The application of molecular genetics to the brain has led to dramatic progress, allowing the identification of defective genes in over 50 neurological diseases. Molecular techniques provide us with powerful methods of manipulating molecules and cells that can be used for therapy and for generating animal models of disease which can be used to provide new knowledge and to test new therapies. Broad advances in basic research has given us information about ion channels, receptors and growth factors, about the ability of nerve cells to grow and to regenerate; and about the circuits that make up our brains. The development of sophisticated imaging techniques allows us to pinpoint diseased areas of the brain and to examine the activity of the normal brain during speech, learning and movement. New computational and cognitive methods allow us to study the biological basis of learning, memory and simple behaviors. An investment in brain research will lead shortly to dramatic new therapies and will lay the foundation for future advances.

IMPROVING HEALTH OF THE NATION'S CITIZENS

Mr. Stokes: What opportunities are ready to be exploited and what are the potential benefits for improving the health of the American people?

Dr. Varmus: Major opportunities exist in the areas of prevention, treatment and rehabilitation. Investigation of risk factors in stroke, in epilepsy and in infants susceptible to neurological disease will increase our ability to recognize and treat those most at risk. In many cases, simple medications or dietary changes will have major effects on health. New treatments for neurological disorders will arise from the development of methods of gene therapy, and of using altered cells to produce therapeutic molecules. Rehabilitation will arise from our increased understanding of the factors controlling neural regeneration, and of our ability to generate sophisticated neural protheses to replace lost function.

The partnership of basic and clinical research is especially promising in the neurosciences. The ability to locate genes and understand their function allows us to develop treatments, such as enzyme replacement, as well as to explore the prospects for gene therapy. The remarkable conservation of genes across species means that we can study complex functions in relatively simple organisms. We can expect to see significant progress in disorders as varied as Alzheimer's disease, muscular dystrophy, and mental illness. Other important work on the life and death of nerve cells is producing important and often surprising information about how selected populations of nerve cells are maintained and why they degenerate, with implications for disorders of movement, sensory processing, and cognition, as well as for recovery from trauma, stroke, and exposure to neurotoxins.

NEUROSCIENCE FUNDING

Mr. Stokes: What is the extent of the NIH's investment in this particular area of research in FY 1996?

Dr. Varmus: The 1996 budget request includes $2,098,711,000 for NIH funding of research in the neurosciences.

Mr. Stokes: How does this compare with FY 1995?

Dr. Varmus: The FY 1995 estimate is $2,031,621,000.

Mr. Stokes: How does this compare with FY 1994?

Dr. Varmus: In FY 1994 NIH spent $1,953,822,000 for neuroscience research.

MINORITY HEALTH ISSUES

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health indicated, in testimony before the Committee this year, that the Department is enhancing its efforts to close the health disparity gap. While this issue is complex and a multiplicity of factors contribute to the disparity including life style and access to health care, biomedical research does have a key role to play in helping to close the gap. What are the most significant activities underway at the NIH to help address this national problem?

Dr. Varmus: The Minority Health Initiative (MHI), which was launched in FY 1992 is supporting a series of multi-year research studies designed to shed light on some of the most important disparities in minority health status. The MHI has five components that address significant minority health issues across the lifespan. The Initiative is administered by the ORMH and the research studies are managed by the component Institutes of NIH in partnership with the ORMH.

The Infant Mortality component of the MHI supports community-based epidemiological and clinical research to address the problem of the unacceptably high infant mortality rate in Washington, D.C. Despite overall improvements in national infant mortality rates, African American infants continue to be twice as likely as white infants to die within the first year of life. This problem can clearly be seen in the District of Columbia, a predominantly African American city that has the Nation's highest infant mortality rate.

The Minority Children component focuses on research on injury-related morbidity, lead poisoning, asthma, learning disorders, and hearing and speech impairments among minority children ages 1-9. This component includes a major research initiative to address the etiology and treatment of a variety of environment-related health problems in minority children.

The Minority Youth component focuses on evaluating and comparing various community-based interventions to decrease violence-related injuries and deaths, sexually transmitted diseases (STDs), and unintended pregnancies in minority youths ages 10-24. Minority youths are at greater risk for suicide, homicide, substance abuse, unintended pregnancy, and STDs, including AIDS. Homicide is the leading cause of death for minority youth. This initiative also supports a comprehensive community-based program to include minority adolescents with HIV in clinical studies of novel HIV treatments.

The Young Adult Component supports a variety of research projects, both intramural and extramural, related to the health problems and behaviors of young minority adults. Research projects focus on minority health problems such as kidney disease, hypertension, diabetes, obesity, glaucoma, hemochromatosis, systemic lupus erythematosus, alcoholism, and AIDS. Studies to examine the recruitment and compliance of minorities in clinical trials are also supported.

The Older Minority Americans component of the MHI funds research centers dedicated to the study of diseases and conditions that lead to ill health and disability in aging minority populations. Six centers are currently studying such conditions as hypertension, cancer, diabetes, and arthritis.

The following are examples of research projects supported under the MHI on particular diseases that cause a disproportionate burden of ill health and disability among minority populations.

Systemic lupus erythematosus (SLE), a painful disease of the immune system that primarily afflicts women, is three times as common among African American women than among white women. The National Institute of Arthritis, Musculoskeletal, and Skin Diseases, in partnership with the ORMH/MHI, is supporting basic, clinical, and epidemiological research projects to determine the causes of SLE and to investigate why the disease is more common in women and minorities. Two Specialized Centers of Research on SLE have been established to provide additional focus on the problem.

Noninsulin dependent diabetes mellitus (NIDDM) and its complications constitute a major health problem in several minority populations. Hispanic Americans have three times the risk of developing NIDDM as non-Hispanic whites, while Native Americans are 10 times more likely than whites to develop NIDDM. In partnership with the ORMH/MHI, the National Institute for Diabetes and Digestive and Kidney Diseases is giving a high priority to research studies aimed at identifying genes and genetic markers associated with NIDDM in minority populations. Thus far, several potentially important genetic markers have been identified in African Americans with NIDDM. Studies of Creole Indians with NIDDM have identified a significant association with a particular gene that is not seen among other Indian subpopulations with NIDDM. These findings are important because the discovery of genetic markers for NIDDM in particular minority groups will allow a more focused effort to better understand the underlying mechanisms of this disease so that appropriate treatments may be developed.

Drug Abuse is a significant health problem among minority populations. Minorities are more likely than nonminorities to die as a result of drug abuse, to suffer severe drug-related illness, to receive inadequate treatment, and to be involved in drug-related violent crime. The National Institute on Drug Abuse, supported by the ORMH/MHI, is aggressively engaged in a broad spectrum of research, prevention, treatment, education, and training programs to meet the special needs of minority populations in regard to drug abuse.

Health problems associated with exposure to environmental contamination, including respiratory diseases and lead poisoning, are more common among minorities and low-income groups than among the population as a whole. The National Institute for Environmental Health Sciences, in partnership with ORMH/MHI, has initiated the Developmental Centers Program to support multidisciplinary research centers that utilize state-of-the-art science to address the environment-related health problems of economically disadvantaged and/or underserved populations. The Center for Bioenvironmental Research, a collaborative effort between Tulane University and Xavier University--a historically black institution--is the first such center to be funded. It has begun a clinical trial to study the effects of lead exposure in African American children, as well as studies of the health effects of lead in pregnancy. The National Institute of Allergy and Infectious Diseases, in partnership with ORMH/MHI, is supporting studies of asthma in Hispanic and Asian populations.

IMPACT OF FTE FREEZE

Mr. Stokes: Is the Institutes currently under a FTE freeze and, if so, how long has it been under this freeze?

Dr. Varmus: The NIH had been under a PHS-agency wide hiring freeze limiting hires to personnel within the Public Health Service since December 1993. The freeze was lifted in February 1995.

Mr. Stokes: How is the freeze impacting operations?

Dr. Varmus: As a result of the freeze, NIH under-utilized its FY 1994 employment target by 568 FTEs. Ranks of doctoral scientists are shrinking; since September 1993, NIH has lost 7% of its strength. Replacement efforts have been slowed significantly by the hiring freeze. Intramural laboratory efforts have been delayed, set back, or terminated. Examples include the cancellation of a program on the biomechanics of balance in Parkinson's disease; a slowdown in the progress of drug development for Alzheimer's Disease; and a slowdown in gene therapy activities. Delays in replacing vacancies have meant increased workloads for remaining staff and have had a detrimental effect on employee morale.

FEDERAL ROLE IN SUPPORTING INTRAMURAL RESEARCH

Mr. Stokes: In light of continuing fiscal constraints and having also been an extramural researcher, in your professional judgement, why must the federal role in intramural research continue?

Dr. Varmus: A Committee of External Advisors of the Director's Advisory Committee, NIH, addressed this issue in its report dated April 11, 1994. This report gave strong support to a vital intramural program which can compliment research activities in the extramural community.

The External Advisors noted of several unique characteristics of the Intramural Research Programs: "These [characteristics] include relatively long-term and stable funding of research programs, the availability of the Clinical Center's patient investigational facilities, few or no distractions from research for scientists, and a primarily retrospective rather than prospective review process for determining scientific quality and the funding of research." The Advisors emphasized "that a strong Extramural Research Program requires a strong Intramural Research Program and quality -- not necessarily uniqueness, should be of the highest priority in determining support for the Intramural Research Program." The

Advisors developed a series of recommendations aimed to create more uniform and consistent processes for setting priorities and ensuring quality across the NIH Intramural Research Program.

As characterized by the External Advisors, the Intramural Research Program is an integral part of the overall biomedical research efforts sponsored by the NIH and contributes both to diversity and vitality of the enterprise.

FUNDING FOR LEARNING DISABILITIES RESEARCH

Mr. Hoyer: Recently, some NIH-sponsored research at Johns Hopkins University, the Kennedy-Krieger Institute and the National Children's Medical Center in Washington DC has shown some dramatic and unexpected results with broad implications on the medical aspects of learning disabilities. This research has focused on children with neurofibromatosis type 1 but has implications for many other types of learning disabilities. Does NIH expect to continue funding this project?

Dr. Varmus: The Johns Hopkins Learning Disabilities Research Center (LDRC) has just completed its first five year funding cycle. The Hopkins group has just submitted an application for a competitive renewal for continued study of LD, neurofibromatosis type 1 (NF1), Fragile X Syndrome, and Turner's Syndrome. Given the significant discoveries made by this research group during the first five year period, the probability of an enthusiastic peer review is good. However, this is an open competitive process and funding of the Hopkins application will depend on how it compares with the other applications and the available funds.

Mr. Hoyer: Does NIH (NICHD) have any plans to expand this study to adults with learning disabilities?

Dr. Varmus: Yes. In fact, the Johns Hopkins LDRC has already conducted a number of studies with adults manifesting NF1 and LD, as well as adult females presenting with Fragile X syndrome and LD. The Yale LDRC and the Colorado LDRC also have substantial samples of adults with LD who are being studied via neuroimaging and genetic methodologies to uncover the biological bases for different types of LD. In addition, the NICHD funded study at the Bowman Gray School of Medicine has been studying a large group of adults with dyslexia and has one of the largest neuroimaging and genetic data sets on these individuals.

PUBLIC HEALTH EDUCATION PARTNERSHIP

Mr. Hoyer: You have told us today of the importance of public information and outreach in improving the nation's health. In fiscal year 1994, the Committee appropriated funds to the NIH Office of Research on Women's Health to participate in a national women's health public health education program through science museums. The Maryland Science Center has been chosen to be the lead on this project, and Johns Hopkins University has agreed to manage the funds without charging any administrative or overhead costs. I understand that these funds have not yet been released. Could you give me an update on the status of this project?

Dr. Varmus: In FY 1994, the Conference provided $11,138,000 to the NIH Office of Research on Women's Health, an increase of $375,000 over the $10,763,000 budget request. In response to the House Committee's directive, the Office initiated efforts to use this increase to develop a national public education program on prevention of women's health problems, through the National Museum of Health and Medicine, Armed Forces Institute of Pathology, in conjunction with the Maryland Science Center.

The NIH has begun the process to enter into an interagency agreement with the National Museum of Health and Medicine. This will enable the Maryland Science Center to proceed with this project. However, early this year, a satisfactory agreement could not be reached with the involved parties--outside of NIH--and the transfer of funds were delayed at the request of the Maryland Science Center. We will continue to pursue this effort and expect that an agreement will be reached in the near future.

Mr. Hoyer: As we seek alternative and creative methods of reaching the American public with the message that our investment in biomedical research is producing tangible results, should we be looking more to science museums and informal education institutions for assistance?

Dr. Varmus: NIH is concerned with public communications in a wide variety of contexts. Science museums and informal education programs are important players in a nationwide effort to improve the public's understanding of the promise and accomplishments of biomedical research. They are expanding their efforts by means of travelling exhibits, school partnerships, and electronic communications. As they reach larger audiences and focus more on biology and medicine, informal science programs and science museums become potential partners with NIH in an effort to increase public awareness. On the NIH campus in Bethesda, the NIH Office of Communications operates a science center, the Visitor Information Center (VIC), which features both an array of interactive exhibit and an actual operating "Learning Lab" where visitors can take part in experiments. The "VIC" was the springboard for a travelling NIH Centennial exhibit that was widely shown across the country. More recently, the NIH's National Eye Institute has developed a major travelling interactive exhibit, entitled "Vision," which is being presented to a national audience via the science museums and centers.

The NIH Office of Science Education also conducts a number of informal science programs that bring local middle and high school students into NIH laboratories for hands-on learning experiences. These include: the Biomedical Research Advancement Saturday Scholars (BRASS) program, the Medicine for the Public program, the NIH Mini-Med School, the NIH Science in the Cinema program, and the NIH/Howard Hughes Medical Institute/Montgomery County Public Schools Student and Teacher Internship Program.

Mr. Hoyer: What sort of cooperative efforts and partnerships is NIH developing with such institutions?

Dr. Varmus: In 1991 the NIH developed the Science Education Partnership Awards (SEPA) grant program which supports the development of innovative programs that join working scientists and educators in enhancing science education for the public. A number of projects originally supported through this program included science museums and informal science education organizations. These projects included: a partnership between the New York Hall of Science and the Association of Science and Technology Centers to develop a national travelling AIDS exhibit and education program; a partnership between the Public Television station WQED/Pittsburgh and five medical research centers to develop a national video education program based on the PBS series "The Universe Within"; and a partnership between the American Association for the Advancement of Science (AAAS) and over 500 churches in the AAAS Black Church Network to develop a set of hands-on biology activities for use in after-school programs, health fairs, community health days, and exhibits in malls and grocery stores.

For the past few years, the NIH Office of Science Education (OSE) has worked with the Maryland Science Center to support many of its education programs. The OSE has provided financial support for the Center's annual Maryland Science Week activities and in 1993 sponsored a play-writing contest as part of the festivities. The contest challenged Maryland students to write a one-act play on a scientific theme, the winning play was then produced and presented at the NIH. The Director of the OSE currently serves on the Maryland Science Week Advisory Board.

FUNDING DISEASE AREAS

Ms. Pelosi: In follow-up to today's hearing, could you please explain the problems of comparing research spending for one disease with research spending for another disease?

Dr. Varmus: Comparisons of NIH research funding among different diseases are problematic because they tend to understate our interests and commitments to advancing knowledge and understanding both of particular diseases as well as human health in general.

First and foremost, much of the research supported and conducted by NIH is basic in nature, and not disease-specific. In some cases, an important target of research in understanding normal developmental, physiological, or even population-related processes to better understand, identify, prevent, and treat a range of problems. Consequently, disease-specific research figures tend to understate the contribution of basic research to the understanding of disease development.

Second, because of the interdependent nature of scientific knowledge, there are significant overlaps among different areas of research, even when they are targeted. For example, cancer researchers made the discovery that the drug AZT impedes the activity of the AIDS virus. Thus, in this case, funding for cancer yielded a discovery that is particularly useful to other disease area--the treatment of AIDS--but provided a lesser immediate benefit to the further understanding of cancer. Again, disease-specific spending figures generally do not reflect the overlapping discoveries and contributions of other fields of study.

Finally, scientific advances and opportunities play a critical role in the decision making process at NIH. A recent research advance will often create greater scientific opportunities for R&D in one disease area than in others. Likewise, a lack of knowledge regarding underlying physiological processes can inhibit the development and evaluation of diagnostic and therapeutic technologies for other conditions. Thus, varying research support figures reflect the level of scientific advances and opportunities in different areas, rather than a judgment about the relative importance of different diseases.

BEHAVIORAL RESEARCH

Ms. Pelosi: To what extent is AIDS a "behavioral" disease?

Dr. Varmus: HIV/AIDS in first and foremost an infectious disease. It is powerful and virulent, and moves from person to person and from group to group in ways that are more complex than the engagement in or avoidance of particular behaviors. Although we can identify a set of behaviors that increase the risk of HIV transmission and that are important to modify -- sex with an infected partner, use of infected drug injection equipment, use of contaminated blood products -- behavior change alone will not abate the AIDS epidemic.

Moreover, many of the other chief causes of morbidity and mortality, such as heart disease, lung cancer, and diabetes, are similarly affected by behavior, for example dietary choices, smoking, and exercise, but also will not be eradicated by behavior change alone.

Therefore, it is important not to think of any disease as a "behavioral" disease, but rather to look at the behavioral component of infectious, inheritable, and other acquired diseases as part of an overall health promotion and disease prevention strategy.

Implementation Plan: Health and Behavior Research." A few selected examples of recent research findings are listed below.

At the National Heart, Lung, and Blood Institute (NHLBI) advances have been made in understanding the relationship between depression and coronary disease and the need to treat patients for their psychosocial as well as for their traumatic illness. Results of clinical studies indicate that providing treatment for the psychosocial aspects of coronary diseases, such an depression, prolongs survival. NHLBI has made progress in understanding how mental stress affects functioning of patients with coronary disease. In the area of health quality of life, NHLBI has improved its knowledge of what contributes to full resumption of function in patients following coronary by-pass surgery as well as how quality of life influences treatment of children with asthma and individuals with sickle cell disease. In the area of cystic fibrosis, NHLBI has been developing methods for improved self management of cystic fibrosis patients and this will contribute to improved health outcomes and better psychological adjustments of these patients.

National Institute of Child Health supported investigators studying the relationship between sugar intake and hyperactivity found no effect of sugar, aspartame, or saccharine on children's behavior, not even on the behavior of children who were identified as being sensitive to sugar by their parents. This study supplies the scientific evidence to end twenty years of controversy.

The National Institute on Aging (NIA) in currently supporting research on the nature, extent, and outcomes of self-care behaviors in diverse populations of older people in order to develop social and behavioral interventions for encouraging health and effective functioning in later life. Inappropriate self-care can lead to delays in seeking needed care or conversely, overutilization of the medical care system for trivial symptoms. Recent NIA studies on medical self-care dispel myths that suggest older people are incapable of recognizing the significance of illness symptoms and that they are more prone than younger persons to use inappropriate strategies that could exacerbate conditions. While most older people have a good knowledge of symptoms and risks, NIA studies show there is a need for greater health education regarding the causes and consequences of common non-specific symptoms--such as fatigue, sleep difficulties, headache, and stomach pain-- which are often erroneously attributed to age or stressful situations.

At the National Cancer Institute (NCI) a community-based study to encourage cigarette smokers to quit achieved modest success in helping light-to-moderate smokers stop smoking. The community intervention was unable, however, to increase the rate at which heavier smokers--those who smoked 25 or more cigarettes per day-ended their addiction. Thus, while significant progress has been made in reducing smoking rates, more research is needed to develop equally effective interventions for more heavy smokers, who are at the greatest risk for the health consequences of cigarette smoking.

At the National Institute of Mental Health (NIMH) research is being conducted on lower back pain. In one study a major focus was to evaluate whether certain psychological testing will serve as useful predictors for those acute low back pain patients who subsequently develop chronic disability problems. Although the overall results are not yet available, a number of interesting findings have been obtained. In a group of 200 chronic low back pain patients substance abuse and anxiety disorder were found to precede chronic low back pain whereas major depression developed either before or after the onset of low back pain. These are the first findings which indicate certain psychiatric syndromes appear to precede chronic low back pain. Another NIMH study demonstrated higher prevalence rates of psychopathology in chronic and then in

Ms. Pelosi: To what extent are other diseases being studied at NIH behavioral?

Dr. Varmus: The study of human behavior is an essential component of the research effort required to address a large number of crucial health issues. Biobehavioral issues cut across all areas of basic and clinical research on health and disease and are a critical part of the mission of the National Institutes of Health (NIH). Through an understanding of the structure and function of the brain, the neural bases for memory, cognition, emotion, perception, performance, and behavior can be uncovered, and approaches to the amelioration, prevention, and treatment of diseases and disorders improved. Behavioral and lifestyle factors are major causes of morbidity and mortality in the United States (Healthy People 2000: National Health Promotion and Disease Prevention Objectives, 1990) and significantly contribute to all 10 of the leading causes of death in America. Behavior in integrally entwined in health and disease in several key ways: (1) as a cause of illness and as a risk factor through health-damaging behaviors, such as alcohol and other drugs, diet, high-risk sexual practices, smoking; (2) as a cofactor in disease progression by modifying the course of illnesses; (3) as a consequence of illness, with a co-occurring depression anxiety, substance abuse, and other psychosocial impacts of chronic illness; and (4) as a method of treatment and prevention. Additionally, changes in behavior may be a manifestation of mental and addictive disorders and direct injury to the central nervous system, affecting one out of five Americans over their lifetimes. Mental and addictive disorders, neurological diseases, sensory and communication deficits, and problems of development and aging reflect the pervasive influence of the brain on multiple body systems, underscoring the critical importance of molecular biology, structural biology, neuroscience, and the behavioral sciences to increasing our understanding of alterations in human behavior.

Diseases and functional conditions such as heart and lung disease, cancer, arthritis, geriatric frailty, dental caries, alcohol, drug abuse, and AIDS are behaviorally involved. Other examples include: unintentional injuries in regard to mental retardation; non-compliance with prescribed treatments for TB, diabetes, or asthma patients; and increased infant morbidity and mortality due to smoking by the mother during and after pregnancy.

Ms. Pelosi: Located within the Office of the Director is the Office of Behavioral and Social Science Research. What are the planning responsibilities of this office?

Dr. Varmus: The Office of Behavioral and Social Sciences (OBSSR) will provide leadership and direction in the development, refinement, and implementation of an NIH research strategy for the conduct and support of behavioral and social sciences research. Specifically, the OBSSR will: (i) develop a standard definition of the behavioral and social sciences; (ii) develop an overall plan to evaluate the importance of multifactorial lifestyle determinants that interface with medicine; and (iii) foster comprehensive research and research training programs to identify individual, familial, social, and environmental factors that contribute to the promotion of good health and the prevention of disease and disability.

ADVANCES IN BEHAVIORAL RESEARCH

Ms. Pelosi: What advances have been made in the last year in behavioral science?

Dr. Varmus: Behavioral and social research is supported widely throughout the NIH. The nature and extent of this research were most recently reported to the Congress in 1993 in a report titled "NIH acute low back pain patients. In particular, chronic lower back pain patients had higher rates of major depression, substance abuse and personality disorders. Moreover, the chronic low back pain patients also had higher rates of premorbid psychopathology.

PROPOSALS TO CONTAIN INDIRECT COSTS

Ms. Pelosi: Please provide a description of any proposals from the Administration with regard to indirect costs which may effect the 1996 Budget.

Dr. Varmus: The Administration has proposed several modifications to OMB Circular A-21 that will have a constructive effect on the stabilization and streamlining of indirect costs. However, the changes do not represent actual reductions of indirect costs reimbursement in FY 1996. Certain changes will have a positive economic effect over the next several years, such as the elimination of special studies for the determination of utility costs, the elimination of dependent tuition benefits, and the requirement to use the rate in effect at the time of the award throughout the life of the project.

Even more importantly, the Administration has announced additional changes that will be developed over the next year. These changes include the benchmarking of facility construction costs so that any new space costs must meet these standards or be reviewed by a Federal panel. The ratio for allocating utility costs to research will also be benchmarked so that it is standardized among institutions. The announcement also proposed the development of a standard methodology for the uniform treatment of specialized service centers, including animal care centers and biohazard facilities.

All of these changes will have a salutary effect on indirect costs over the next several years. These changes will streamline and standardize the rate negotiation process and stabilize the costs so that they are supporting the essential resources necessary to the conduct of research.

JUSTIFICATION OF THE BUDGET ESTIMATES

The Department of Health and Human Services
The Public Health Service
National Institutes of Health

FY 1996 CONGRESSIONAL JUSTIFICATION
OVERVIEW

Introduction

As the preeminent biomedical research organization in the U.S., NIH and its twenty-three Institutes, Centers and Divisions (ICDs) provide world leadership in the field and are committed to supporting initiatives having the greatest potential for improving health, reducing the risk of disease, and, ultimately, enhancing the quality of human life. Through the conduct, support and promotion of outstanding biomedical research, NIH seeks to expand fundamental knowledge about the nature and behavior of living systems, to apply that knowledge to improve the health of humans, and to reduce the burdens of disease and disability. Some major discoveries create opportunities for new strategies in the diagnosis, treatment and prevention of disease while others result in advances in the application of strategies for treatment and prevention. Other advances enhance our understanding of the complexities of human health and behavior, and provide a foundation for future scientific progress. A critical factor is an understanding that medical progress rarely occurs without the sustained pursuit of basic science.

As early as 1887, national concern for the elimination of such devastating diseases as tuberculosis, typhus, cholera, smallpox, and diphtheria prompted federal support for basic biomedical research. This growing national concern led to the establishment of NIH. Today NIH supports more than 50,000 scientists working at 1,700 institutions across the U.S. Of the sixty-nine U.S. scientists awarded the Nobel Prize in physiology or medicine since 1945, more than two-thirds were supported by NIH before winning the prize including the FY 1994 prize winners, Dr. Martin Rodbell, a scientist emeritus in the NIH intramural program, and Dr. Alfred Gilman, an NIH grantee at the University of Texas Southwestern Medical Center. Their research on G proteins, key components of the communication system that regulate cellular activity, provides the research community with insights into diverse diseases including diabetes, cancer, and cholera. The recognition given such scientists highlights the vital role of basic research in the development of innovations in biomedicine.

Assessment of Research Benefits

The identification of future benefits of current research has become an impossible task for NIH as a result of the transformation of biomedical research. The nature of biomedical research and the promise of biomedical innovation has become more complex and far-reaching than was imagined 50 years ago. Throughout the nation's 107-year history of support for biomedical and later, behavioral research, scientists and physicians have developed effective methods for preventing and treating many diseases. Early in the twentieth century, the most dramatic successes affected public health and resulted from research focused on isolating the causes and devising the preventatives and cures for common and often deadly bacterial infections including diphtheria, tetanus, pertussis, typhoid fever and typhus; and for deficiency disorders such as diabetes and pellagra. Federal support for biomedical research and strategies to improve public health expanded as the eradication of devastating diseases provided tangible evidence throughout society of the benefits of such research.

In the past quarter century, following these dramatic successes, national attention shifted to the more complex and intractable problems associated with viral and genetic diseases and behavioral disorders. This shift helped to recast biomedical research from studies targeting specific diseases to multidisciplinary studies affecting a number of diseases. Further, this shift provided scientists with a deeper understanding of human health at a molecular and genetic level. Contributions from scientists across a variety of biomedical and behavioral disciplines aided in the development of the most effective approaches to characterize the complex patterns of the immune system, the control and expression of genetic material and neurological function. As researchers in one discipline provide discoveries that expand basic biomedical knowledge, scientists in other disciplines are able to apply these discoveries to the development of rational methods to prevent, diagnose and treat physiological and behavioral diseases and disorders. Future benefits of these biomedical innovations are expected, at a minimum, to provide effective treatments and cures of diseases that, currently, are extremely costly in terms of medical care, loss of productivity, and human suffering.

NIH is committed to seeking the most effective approaches to improve human health. However, as biomedical and behavioral problems and scientific approaches become more complex, the predictions and assessments of the benefits of research discoveries become more difficult. As a result, measures and methods to represent long-term benefits of research continue to elude analysts for a number of reasons. In a recent article examining the social and economic merit of biomedical research (*Science*, Kirschner, Marincola, and Teisberg, October, 1994) the authors note that biomedical innovation is "undervalued" in current models for analyzing research benefits. These models are not designed to calculate the impact of past advances that eliminated diseases such as small pox and polio on modern medicine and on savings in health care cost. Further, the elusive nature of this issue is characterized by the lack of adequate measures to determine the social and economic benefits that ensue as medical advances are rapidly incorporated into standard practice, and by the inability to assess the implications and applications of basic research on these emergent disorders.

Basic research provides the core of knowledge from which scientists develop further innovations and applications. Speculating the impact of current research on future advances across diverse scientific disciplines can be misleading since there is no accurate way to predict the timing or the range of influence of research discoveries. The following examples of NIH-supported research reflect this unpredictability and the potential range of influence:

- In 1984 Dr. R. Bruce Merrifield was awarded the Nobel Prize in Chemistry for his research in the development of solid phase peptide synthesis which has been applied to many biochemical and biological problems, including the development of drugs for the treatment of Paget's disease by commercial entities and vaccines against malaria, hepatitis, and diabetes.

- Dr. George A. Olah received the Nobel Prize in chemistry for his research in the structure and function of highly reactive molecules, involved in natural and synthetic chemical processes. This was vital to the development of our understanding of the mechanism of enzyme reactions in a broad range of physiological processes. From this Dr. Olah developed reagents and scientific methods used today in the chemical synthesis of a wide variety of materials, from gasoline to pharmaceuticals.

- In the 1970s, scientists provided the first comprehensive description of the sequence of hormonal interactions during the menstrual cycle which laid the foundation for modern reproductive endocrinology and new approaches to infertility and contraception.

Recent discoveries are expected to yield many similar results. However, it will take years of research to uncover the full-range of benefits from promising recent breakthroughs such as the determination of the three-dimensional structure of myosin, the protein critical to motion, energy, and force in nearly all living things. While an accurate measure of the social and economic impact of biomedical research on national interests cannot be made immediately, many tangible benefits can be noted. NIH continues to examine the most current health care advances and to estimate cost savings related to its studies. The following are selected examples of this analysis:

- Research has led to the development of the *Hemophilus influenzae type b* (Hib) vaccine which can be given safely to infants as young as two months of age, while overcoming weak immune responses in infants and children. This vaccine promises to eliminate the 10,000-15,000 cases of *Hib* meningitis each year, the most common cause of acquired mental retardation in the U.S. This disease is responsible for nearly 800 childhood deaths a year. Cost savings could reach $460 million annually.

- Clinical trials to evaluate the efficacy and safety of Zidovudine (AZT) in the prevention of maternal-fetal transmission of HIV revealed that use of AZT reduced transmission of HIV infection have shown that such transmission is reduced by two-thirds. Potential cost savings may reach $172 million annually.

- A $5 million investment in the development of an antiviral therapy, Acyclovir, in newborn infants suffering from neonatal herpes simplex (HSV) infection can significantly reduce the direct cost of treating HSV as well as costs indirectly associated with this infection, namely premature mortality and severe neurological impairment. The estimated annual cost saving is $160 million.

- A recent research breakthrough showing that peptic ulcers can be caused by a bacterium, *Helicobacter pylori*, has resulted in a simple cure by using inexpensive antibiotics. Savings may reach $700 million yearly when compared to the therapies used prior to this discovery.

- Recently, scientists developed the first effective treatment for spinal cord injury. Patients treated with *methylprednisolone* within the first eight hours after injury recovered more motor and sensory function than did patients who did not receive the drug.

Further, basic biomedical research continues to have a significant impact on the nation's economy by leading to high-quality, long-term employment for more than one million people in scientific and related areas. It has fueled the growth of the biotechnology and pharmaceutical industries to more than $100 billion yearly, spawning opportunities for U.S. industry to compete in global markets, and expanding opportunities in the U.S. labor market by producing more than 200,000 high-paying, highly-skilled jobs. For example, the discovery and characterization of the LDL receptor by NIH-supported investigators spurred the development of the HMGCoA reductase inhibitors by pharmaceutical companies. These agents, such as *simvastatin*, lead to the up-regulation of the LDL receptor and the reduction of the LDL plasma concentrations. They have now been shown to reduce markedly fatal and non-fatal heart attacks and total mortality in patients with prior coronary heart disease.

In a 1991 survey, biotechnology companies confirmed the importance of this support by overwhelmingly identifying further support for basic research as critical to the industry's health and success. Research collaborations between NIH and the private sector continue to be a critical component of NIH intramural research efforts. Cooperative Research and Development Agreements (CRADAs), a mechanism created by the 1986 Federal Technology Transfer Act, enhance and facilitate such collaboration through which NIH scientists and commercial firms can expedite the transfer of expertise and technology and encourage the development of improved health care products, processes and services. Since 1986, NIH has supported 206 CRADAs. These agreements have proven to be cost-effective and enable companies to leverage their own research and development efforts. In turn, the stewardship of public funds for support of biomedical research is maintained and national economic and social interests are strengthened.

Government Performance Review Act of 1993

NIH has formed working groups comprising Planning and Evaluation Officers and Budget Officers from the Institutes, Centers and Divisions to identify requirements of the Government Performance Review Act (GPRA) as they relate to NIH. Currently, the working groups are identifying goals and strategies and examining issues related to the development of effective measures of performance for research as outlined in the GPRA.

NIH Streamlining Process

The NIH has developed a Streamlining Process designed to maintain its research capability and to assure the quality of its scientific and clinical programs while accommodating personnel reductions, changing organizational and administrative procedures, and program operations. Components of the Process and the Plan that will be formulated are:

- ***Organizational and Systems Changes*** - Included are the possibility of clustering decentralized administrative services; exploring new mechanisms to provide administrative services; and the centralization of some specific grant-related data operations.

- ***Information Technology*** - Reengineering NIH administrative processes and the technologies that support those processes is underway. This process includes the development of a consensus architecture, more effective central support of Local Area Networks, and a commitment to the NIH communications infrastructure in order to meet demand.

- ***Redesign of Support Systems*** - The possible redesign of NIH's administrative database will be explored and issues related to budget and personnel will be addressed.

- ***Intramural Research Program*** - Opportunities for streamlining within the Intramural Research Program (IRP) include the sharing of resources and a review of intramural scientific programs designed to assure greater efficiency in the use of such resources. The IRP is particularly vulnerable to the effects of downsizing, because it depends to a large extent on limited-time appointments for scientists in training.

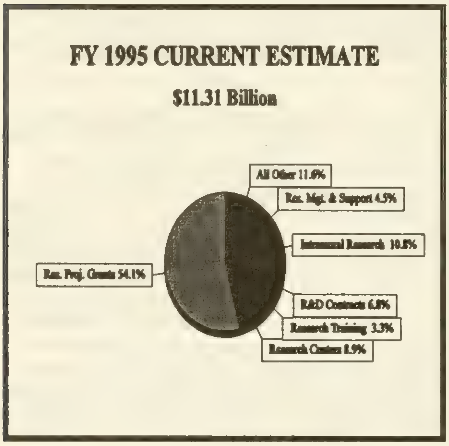
- ***Extramural Research Program*** - A series of initiatives have been proposed and subsequently been endorsed by the Department of Health and Human Services (DHHS) in designating the NIH Extramural Research Program as a Reinvention Laboratory. These initiatives focus on changes in processes for the receipt, review, award and post-award management of applications for NIH grants which support research and research training.

In late summer, the NIH Director convened a forum of ICD Directors and key staff to re-evaluate the future direction of NIH in light of declining resources. Relevant topics included the sharing and pooling of scientific resources, achieving efficiency through organizational and administrative changes, reengineering of administrative systems and the continuing reinvention of the extramural programs.

Intramural Program Review. In response to a request from Congress, an extensive review was undertaken of the IRP in 1993-94 by a distinguished panel of advisors from academia and industry. The Report of the Extramural Advisors to the Intramural Program has been submitted to the House Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education and Related Agencies. The panel reviewed the role, size, and cost of the Intramural Program, and its relationship to the extramural research program. It recommended a process for allocating resources to and among the intramural programs based on a thoughtful analysis of these issues. The Report recommended changes in: NIH-wide policies and practices affecting the appointment and promotion of scientists; recruitment and retention strategies for outstanding scientists; the process by which the research performed by intramural scientists is reviewed; postdoctoral training programs; the use of the patient and research facilities at the Clinical Center; management practices that ultimately affect the quality and quantity of research produced; and opportunities for expanding collaboration between the intramural and extramural communities. The aggressive implementation of these recommendations is currently underway and will assure the quality of the IRP during this period of downsizing. The Intramural Program will continue to provide a foundation of knowledge for all researchers as they pursue biomedical innovations in the diagnosis and treatment of disease and strategies for prevention and health promotion.

Extramural Program Review. As part of the Administration's National Performance Review, the NIH Extramural Program has been designated as a Reinvention Laboratory, enabling it to lead the process of change for grants administration in the Public Health Service (PHS). Currently underway are a series of pilot programs being conducted in specific areas related to grants policy and designed to streamline and reduce the administrative burden associated with the grant application process as well as improve cost management. Pilot programs involving the NIH peer review process include expanded use of triage to select applications for in-depth peer review, modification of the summary statements prepared after review of applications and of the "Just-in-Time" program by which detailed budget and administrative institution data relevant to grant applications is collected only for those applications that are most likely to be funded. The NIH Extramural Reinvention Committee is exploring the feasibility of a modular grant concept in which approved grants would be awarded in modules of given amounts of money, thus eliminating the need for detailed budget submissions by the investigator and review and monitoring of budgets by NIH staff prior to award. In addition, the NIH Extramural Reinvention Committee is examining a proposal to redelegate authorities related to advisory committee administration and grants administration policy, expediting the assignment of competing renewal and amended applications, and exploring the use of teleconferencing to reduce site visits.

FY 1995 BUDGET POLICY



The FY 1995 Estimate for NIH totals $11,305,546,000 adjusted for $7.8 million in rent reduction and procurement savings from streamlining procedures and a reduction of $1 million to reflect a proposed rescission in non-AIDS extramural construction. Including funds for studies of the Acquired Immunodeficiency Syndrome (AIDS), this Appropriation represents an increase of $379,064,000, a 3.5 percent above FY 1994 level. Non-AIDS research will increase by $339,809,000, 3.5 percent above the FY 1994 level.

NIH will continue to respond to the national crisis in AIDS by increasing research support by $39,255,000, 3.0 percent above FY 1994 Actual Budget. The administration of the NIH AIDS Program has been revised in FY 1995 to reflect the mandates of the NIH Revitalization Act of 1993 (P.L. 103-43). AIDS activities will continue to be carried out within the ICDs. However, the appropriation to support these activities will go directly to the

Director, Office of AIDS Research (OAR), who has been authorized to allocate funds to the ICDs for support of AIDS research activities.

The FY 1995 Estimate reflects a commitment to expand specific high priority areas of research: 1) breast cancer research, 2) other women's health research, 3) minority health research, 4) tuberculosis (TB) research, 5) HIV/AIDS research, and 6) technological advances in High Performance Computing.

FY 1996 BUDGET POLICY

Realignment of Grants in the NIH Mechanism Structure

Following a review of the NIH mechanism structure conducted in 1993, NIH realigned research activities to enhance logical groupings of mechanisms and accuracy of the NIH budget display. Specific research grant activities that support investigator-initiated research projects similar to R01 grants, namely, Small Grants (R03) and Development Grants (R21) were shifted from Other Research to Research Project Grants (RPGs). All grants awarded under the authority of the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) set-asides programs are displayed as a subset of Research Project Grants (RPGs) and are excluded from success rate and average cost calculations. This will reduce distortions in the calculations for other RPGs. Such distortions are caused since the size of these awards ranges from Phase I grants with an average cost of $75,000 to Phase II grants with a two-year average cost of $750,000. Finally, SBIR and STTR contracts are displayed parenthetically in the mechanism table to identify all SBIR and STTR activities funded in the NIH mechanism table.

Cost Management

The FY 1996 President's Budget has been formulated in accordance with the cost management principles outlined in *A Plan for Managing the Costs of Biomedical Research*, referred to as the NIH Financial Management Plan (FMP). Through the FMP, NIH intends to balance the necessity of operating within limited federal resources with the goal of expanding fundamental knowledge regarding living systems so as to improve human health. The FMP seeks to achieve these goals by providing the funding stability necessary to maintain momentum in biomedical research advances and by supporting the most meritorious projects as NIH strives to accelerate progress in biomedical research.

Following NIH cost management principles, noncompeting grants will receive committed levels of support based on an average annual direct cost increase per grant of 4.0 percent and the average total cost of competing non-AIDS grants will not increase by more than the Biomedical Research and Development Price Index (BRDPI) over the average cost of competing non-AIDS grants in the previous year. In FY 1992, the high priority and unusually expensive Adult Clinical Trials Groups (ACTGs) were identified as an exception from FMP guidelines related to average cost of competing RPGs. Due to the cycling of ACTGs from noncompeting to competing status in FY 1996, estimated average costs of all competing RPGs will increase by 7.2 percent over

FY 1995. Excluding ACTGs, the average cost increase of all competing grants is 3.4 percent, 0.9 percent below the BRDPI of 4.3 percent, well within cost management guidelines.

Improving the Overhead Payment System for Federally-Sponsored Research

NIH is currently participating on the Research Subcommittee of the National Science and Technology Council's Committee on Fundamental Science. This Subcommittee was charged with the task of reviewing costs of research with special emphasis on reimbursement for research facilities. This review was guided by four major goals: 1) to make the overhead payment system more defensible, equitable and understandable by reducing unexplainable variations in overhead rates to improve incentives for efficiency and to foster consistency in the Federal government's approach to administering the research overhead system; 2) to encourage full and open consultation and participation in the review process from all concerned parties; 3) to focus on facilities as a significant source of rate variation and as an opportunity to reduce such variation; and, 4) to reinforce the Administration's commitment to research. Concurrent with the transmittal of the FY 1996 President's Budget to Congress, the Administration published, in the *Federal Register,* "Cost Principles for Educational Institutions" which outlined fourteen proposed changes to OMB Circular A-21. These proposed changes drew substantially on the work of the Research Subcommittee.

Other Key Issues

Through the leadership of its Director and scientific advisors, NIH continues to lead the Nation in support for basic biomedical research through investigator-initiated research project grants. The FY 1995 and FY 1996 aggregate success rates for all competing research project grants are estimated to reach 24 percent and 23 percent, respectively. NIH relies on new awards to introduce new ideas and to create opportunities for new strategies in the diagnosis, treatment, and prevention of diseases, as well in the practical applications of these new strategies. New ideas in research build on foundations of basic knowledge. Thus, NIH relies on competing renewals to maintain this knowledge base and to allow for full development of research ideas. The pool of competing renewals is limited to grants that previously passed a rigorous peer review process and were among applications selected for funding.

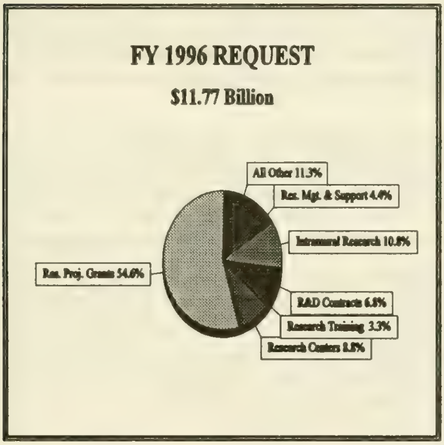
In FY 1996, estimated success rates for new RPGs and competing renewals are 18 percent, and 39 percent, respectively. NIH funding for AIDS competing RPGs follows a similar funding pattern. NIH estimates supporting 31 percent of total AIDS competing RPGS, 25 percent of new and 55 percent of competing renewals in FY 1996. The success rate, excluding AIDS, mirrors that of all RPGs except for those ICs with a large AIDS portfolio.

Of NIH's total competing RPG portfolio, 90 percent of awards are single-investigator RPGs. Single-investigator RPGs include the traditional R01 awards, the FIRST awards (R29) for new independent investigators, and the MERIT award (R37) that provides long-term support to selected investigators with distinctly superior research competence and productivity. The success rate for all single-investigator competing RPGs is 22 percent in FY 1996, similar to total competing RPGs. In FY 1996, success rates for new single-investigators and competing renewal single investigators are 17 percent and 37 percent, respectively. The success rate for AIDS single-investigator competing RPGs is 30 percent in FY 1996, 26 percent for new and 47 percent for competing renewals.

NIH continues to be the nation's leader in support of public education efforts in science and in research training. Recently, NIH sponsored a national conference on ***Communicating Science and Health in the New Millenium***, inviting participants representing a variety of biomedical research, health, and communications disciplines, to participate in panels and working groups to examine NIH's role in the future of public education in science and health.

NIH plays a major role in maintaining the Nation's scientific infrastructure. Further, NIH provides a vital oversight function in the protection of research subjects, the inclusion of women and minorities, and the development of guidelines for issues related to conflicts of interest, technology transfer, and scientific misconduct. The NIH Director continues to review the NIH mission to identify other key issues that contribute to improved agency performance. Among these are: 1) opening lines of communication to provide members of the extramural community an opportunity to participate in the development of NIH policy; 2) formulating effective policy to address new ethical and legal issues emerging in biomedical science; and, 3) strengthening efforts to enrich and diversify the culture of science.

FY 1996 BUDGET OVERVIEW



The FY 1996 Estimate for NIH totals $11,773,066,000, including AIDS, and reflects a $467,520,000, or a 4.1 percent, increase above the FY 1995 Current Estimate. In FY 1996 NIH will decrease Full-Time Equivalents (FTEs) from 16,197 in FY 1995 to 16,135 in FY 1996, in response to the Administration's efforts to reduce the federal workforce.

AIDS research will increase by $72,098,000, and non-AIDS research by $395,422,000, a 5.4 percent and a 4.0 percent increase, respectively, above the FY 1995 Current Estimate. Funds will be directed to high priority research areas previously identified in the FY 1995 Current Estimate, specifically, HIV/AIDS research, TB research, the Office of Research on Women's Health, the

Minority Health Initiative, High Performance Computing (HPCC), breast cancer research, and the continuation of the Secretary's Breast Cancer Action Plan.

HIV/AIDS RELATED RESEARCH: More than 50 percent of the increase in HIV/AIDS research is related to the support of basic science and also will have a significant impact on research in non-AIDS areas. NIH will continue to accelerate research efforts related to HIV/AIDS and to support research to develop safe, effective topical microbicides designed for use by women to prevent sexually-transmitted infections, including HIV infection. The HIV/AIDS Research Summary section of this document provides a complete description of FY 1996 AIDS research priorities.

NON-AIDS RESEARCH: The non-AIDS portion of the NIH budget will include increases to a broad range of disease categories, increases for established high priority research areas, and directed support for special areas of emphasis that have been identified by the NIH Director and the ICD Directors. Some areas of research that will benefit from increases to their research bases include such physically and personally debilitating and financially devastating diseases as cardiovascular disease and stroke, diabetes, cystic fibrosis, mental illness, multiple sclerosis, Alzheimer's disease, osteoporosis, and some cancers.

INCREASES TO HIGH PRIORITY RESEARCH AREAS

Tuberculosis Research [FY 1995 - $51.0 million; FY 1996 - $53.1 million] Opportunities on TB have become critical to the health and safety of the American people as a result of a resurgence in cases of TB in the mid-1980s. NIH will target $2.1 million in FY 1996 to strengthen its comprehensive approach to the prevention, control, and treatment of TB. These efforts include such high priority initiatives as basic research on the genetics of TB, and the physical mapping and DNA sequencing of the M. tb genome.

Office of Research on Women's Health (ORWH) [FY 1995 - $12.8 million; FY 1996 - $17.3 million]: An increase of $4.5 million in the ORWH will strengthen support for biomedical and behavioral research across a wide range of disease areas that predominantly affect women. This investment will be distributed among those Institutes that are currently supporting research in such areas as osteoporosis, ovarian, cervical and breast cancer, lupus, cardiovascular disease and stroke.

The Minority Health Initiative (MHI) [FY 1995 - $58.3 million; FY 1996 - $62.8 million]: Investments in the MHI will be increased by $4.5 million to support the expansion of research on injury-related morbidity, lead poisoning, asthma, learning disorders and vision and speech impairment among minority children, a community-based health behavior intervention program to lower the unacceptably high rates of morbidity and mortality among minority youth, and research in kidney disease, diabetes in blacks and Hispanic women, hypertension in blacks, glaucoma, AIDS and breast cancer.

High Performance Computing & Communications[FY 1995 - $70.6 million; FY 1996 - $78.9 million]: In FY 1996, NIH will provide an $8.3 million increase in high performance computing activities directed by the National Library of Medicine (NLM), the National Cancer Institute (NCI), National Center for Research Resources (NCRR), and the NIH Division of Computer Research and Technology (DCRT). This increase will aid in the expansion of patient care information systems in NLM to link physicians, hospitals and research institutions to improve the quality and effectiveness of treatment and clinical care, refine sequencing databases used in genetic research, and support grants to encourage high-risk technology development.

Breast Cancer Research [FY 1995 - $377.1 million including $10.0 million for the Breast Cancer Action Plan; FY 1996 - $426.2 million including $20.0 million for the Breast Cancer Action Plan]: NIH will provide a $49.1 million increase to support a multi-faceted and coordinated breast cancer research program in basic studies, prevention, treatment, rehabilitation, and community outreach. A trans-NIH collaborative effort will bring multidisciplinary expertise to address the problem of breast cancer. NIH will strengthen support for research in environmental carcinogenesis and occupational risk effects, the development of novel diagnostic approaches to improve breast imaging, basic research efforts that target the genetic aberrations and molecular abnormalities seen in breast cancer, expansion of research efforts in genome mapping, and efforts in cell biology. Support also will be provided for research trainees, and for translational science fellowships to bring scientists to the NIH Intramural Research Program for up to two years to participate in research focused on the fundamental biology and clinical aspects of breast cancer, including its prevention, detection and treatment. NIH will provide a $10.0 million increase for the Breast Cancer Action Plan, for a total of $20.0 million in FY 1996 to emphasize a wide range of actions related to breast cancer as identified in the Secretary's National Action Plan on Breast Cancer.

NIH AREAS OF SPECIAL EMPHASIS

NIH has selected areas of emphasis that promise to yield a greater return on the federal investment in biomedical research. ICDs supporting initiatives within these areas of special emphasis will participate in an ongoing analysis of the research portfolio to ensure that NIH is committing its resources to the best possible scientific initiatives available.

Brain and Brain Disorders Research [+$16.7 million]: NIH will expand this broadly-based research effort to understand the biology of the mammalian brain, and to apply that knowledge to the diagnosis, prevention, and treatment of disease. Recent advances in basic and clinical science, especially in the genetics, cell biology and biophysics of the nervous system, in computational and cognitive neuroscience, and in new methods in diagnosis and treatment, provide the impetus for expanded emphasis on brain-related research. These efforts will dramatically increase our understanding of the biology of the brain, and increase our ability to apply that knowledge to brain disease for human benefit. Areas of particular promise include: molecular genetics to examine neurological and psychiatric disease, and addiction; gene and cell therapy to examine genetic diseases and possible methods of introducing therapeutic molecules; the blood-brain barrier to examine the use of therapeutics, as well as multiple sclerosis, and cerebrovascular disease; life and death of nerve cells to study aging, degenerative diseases of the nervous system, and environmental toxins; and, brain tumors and other disorders of growth regulation.

Disorders of Developmental & Reproductive Biology [+$5.9 million]: The application of genetic and molecular techniques to the study of development in simple animal and plant models has opened new doors to knowledge related to developmental biology and genetics. Current focus is on identifying the complete set of stimuli, genes, and cell-cell interactions which, while operating hierarchically, mediate development. This research is inspired by the recent discovery that all of the master control genes which mediate development in simple animals or plants are also found in humans. This research will build on progress in the past few years in characterizing the earliest signals that promote gene expression during embryogenesis, in identifying the master control genes that specify pattern formation and morphologic identity of the body parts, in defining cell-cell interactions that affect development, in understanding the molecular mechanisms by which gene expression is controlled in the early embryo and in understanding the phenomenon of "programmed cell death." Many questions remain, requiring years of additional effort.

Bone, Muscle and Connective Tissue Disease Research [+$9.0 million]: NIH will accelerate research efforts to ameliorate the degenerative and costly problems associated with osteoporosis, osteoarthritis, and related musculoskeletal disorders.

Mutation and Environmental Cancer Research [+$5.0 million]: NIH proposes to expand support for fundamental research upon which valuable clinical applications for the diagnosis, treatment, and prevention of disease are based. Through increased support for basic science, NIH can pursue cutting-edge technologies in molecular and structural biology and computational chemistry to address several research priorities.

Shared Resources [+$10.0 million]: Through the National Center for Research Resources (NCRR) NIH supports the needs of biomedical researchers by providing a broad array of tools, technologies and materials critical to their research efforts. As the biomedical research community becomes increasingly dependent for the conduct of research on modern instrumentation and leading-edge technology, current levels of support for instrumentation are increasingly inadequate and severely undermine the ability of NIH investigators to carry out high quality competitive research programs. To keep pace with the future instrumentation needs of the biomedical research community, NIH needs to expand support for shared instrumentation immediately.

DNA Sequencing Technology Development [+$10.0 million]: Through the National Center for Human Genome Research, recent scientific advances and technological improvements in DNA sequencing technology have made possible the rapid progress of the Human Genome Project. Support for technology development in DNA sequencing is essential to further accelerate research efforts in human genome research. The development of automated sequencing technology will be supported through a Request for Applications (RFA) which encourages support for research to develop a fully automated, integrated modular system targeted to miniaturization technologies. In addition, NIH would focus on the development of improved informatics tools for data collection and the finishing of sequencing so as to end the greatest bottlenecks in current systems. Additional improvements are required to realize the full power of miniaturized systems.

Gene Therapy [+$10.0 million]: Gene therapy is the stable incorporation, into a cell, of DNA coding for genes not normally expressed, so that the cell and all of its progeny express the new gene, followed by the return of the cell into a patient for therapeutic benefit. Variations of gene therapy are being conducted by a number of Institutes in pioneering clinical trials. This research holds great promise for the treatment of many diseases having genetic bases while expanding the full spectrum of gene therapy techniques, with a special focus on the rapid translation of sophisticated gene-directed technologies from the laboratory into clinical practice.

Structural Biology and Drug Design [+$7.5 million]: NIH will establish and expand databases of solved protein structures, develop instruments and technologies and provide accessibility to scientists, and enhance computer-based technologies to facilitate research in structural biology. NIH will enhance training of investigators capable of bridging the multidisciplinary approaches of structural biology, applied physics, chemistry, computer science, biochemistry and biology.

Prevention Research [+$10.0 million]: Disease prevention research efforts are crucial to reduce the burden of preventable disease and disability in this Nation. Disease prevention efforts offer the most direct means to lessen the enormous personal, social, and economic toll exacted by disease in all its forms--premature birth and severe childhood illnesses, cancer, heart disease, independence-robbing disorders of the elderly, as well as existing and emerging infectious disease threats. Beyond averting or diminishing physical and mental suffering, prevention research can contribute directly to efforts to constrain health care spending.

Computer Technology to Increase Effectiveness of NIH Clinical Programs [+$1.5 million]: NIH will support an initiative to upgrade the Clinical Center medical information system. In comparison to the current system, the proposed system will be more comprehensive and will integrate patient care, clinical research and clinical training more effectively within the NIH campus as well as improving interactions between the Clinical Center and the extramural community. Regional computer nodes equipped for telecommunications will be located throughout the country to serve as the loci for patient evaluation, extramural and intramural protocol monitoring, and interaction with investigators and trainees.

Communications Infrastructure [+$3.0 million]: NIH is committed to streamlining NIH's administrative functions by utilizing modern technology to overhaul the current administrative database. Through this reengineering initiative, NIH will simplify and streamline administrative processes to provide a more efficient means to manage NIH programs.

Buildings and Facilities [+$30.0 million]: NIH will direct resources to fund critical infrastructure and environmental improvements to existing NIH facilities to protect and support ongoing research programs and to insure the safety and health of NIH employees. Of particular importance is the Clinical Center Renewal Program, specifically the concept and design of a hospital addition and associated laboratories as recommended by the External Advisory Committee appointed by the NIH Director. NIH would also begin construction of a critically needed laboratory building to replace obsolete facilities with safe modern research space.

Other Initiatives [+$2.5 million]: Within the Office of the Director, NIH will provide funds to expand the loan repayment and scholarship programs authorized under the NIH Revitalization Act of 1993, and to expand the Academic Research Enhancement Award Program (AREA) that provides opportunities for faculty in educational institutions to participate in biomedical and behavioral research efforts.

SCIENCE ADVANCES

The following examples provide a brief sampling of recent scientific accomplishments that have arisen from biomedical and biobehavioral research supported or conducted by NIH. Virtually, all research that addresses the diagnosis, treatment and prevention of disease is founded on progress in basic research. Fundamental research is exploratory and adds to our broad base of knowledge about how living things function. Because the knowledge is cumulative, advances are usually realized incrementally. Clinical and applied research represents the logical extension of the findings from fundamental research that may ultimately yield significant health care innovations and cost savings. This continuum of progress is reflected in the advances that follow.

ADVANCES IN UNDERSTANDING AND DIAGNOSING CANCER

- **Identification of Breast Cancer Susceptibility Gene.** This year nearly 200,000 new cases of breast cancer will be diagnosed and 50,000 women will die from the disease. The recent cloning of a breast cancer susceptibility gene brings us significantly closer to understanding the origins of this devastating disease. It is an important step toward identifying mutations that can lead to breast cancer, developing tests to identify women who are at increased risk for the disease, and studying the effects of environmental agents that may contribute to many cases of breast cancer. Researchers have also identified the chromosomal region that contains a second familial breast cancer gene and are attempting to identify and clone the relevant gene. Genetic changes in these two genes account for approximately two-thirds of all familial breast cancer, or roughly 5% of all cases.

- **Understanding and Diagnosing Colon Cancer.** Colorectal cancer is one of the most commonly diagnosed cancers in the U.S. As many as 1 in 200 Americans are affected by hereditary non-polyposis colorectal cancer (HNPCC), which also renders them prone to developing cancers at other organ sites. Scientists have recently identified mutations in four genes responsible for more than 90 percent of HNPCC. These genes produce proteins that act as "proofreaders" of DNA, detecting and repairing any mistakes that occur during cell division. When the proofreader proteins are defective, mistakes in DNA are propagated. Some of the mistakes that go uncorrected may be serious; for example, they may lead to uncontrolled cell division and the development of cancer. Further study of this mechanism may shed light on how other cancers develop and may also lead to the development of a diagnostic test for HNPCC. This is the case for another form of inherited colon cancer known as familial adenomatous polyposis (FAP). Investigators are translating their laboratory findings about genetic mutations that lead to FAP into a useful diagnostic tool. They have developed a highly sensitive, non-invasive technique for identifying FAP-specific genetic alterations in colon cells shed into the stool. This screening method could potentially be used for early detection and diagnosis of colon cancer or to monitor for disease recurrence.

- **Genetic Mutations that Lead to Melanoma.** Researchers have identified a key piece in the puzzle of melanoma, an aggressive and often lethal cancer. It was known previously that damage to the p16 gene, which normally suppresses tumor growth, is involved in melanomas that arise spontaneously. Now scientists have demonstrated that mutations in p16 can be passed on from one generation to the next, giving rise to the development of inherited melanoma, which accounts for about 10 percent of all melanoma cases. This finding is an important first step on the path to developing a sensitive diagnostic test to identify individuals especially prone to this fast-spreading cancer, as well as to finding ways to treat the disease early or prevent it altogether.

- **Genetic Defect Linked to Prostate Cancer.** Previous studies have shown that environmental factors are involved in the development of prostate cancer, the most commonly diagnosed cancer among men in the U.S. Scientists have recently discovered a genetic defect in prostate tumors that results in the inactivation of an enzyme needed to protect normal cells from environmental carcinogens. Without the enzyme, cells may be vulnerable to damage from environmental factors, leading to the development of cancer. Further research to elucidate how this critical enzyme is regulated may lead to new diagnostic or treatment measures for prostate cancer.

- **Structure and Mechanism of Tumor Suppressor Protein (p53).** Up to half of all cancers involve mutations in, or the absence of, a protein known as p53, which prevents uncontrolled cell division. Scientists have discovered that p53 works by controlling the production of another protein, p21. In turn, p21 keeps healthy cells from dividing prematurely by regulating an enzyme critical for cell division. Thus, if p53 is mutated or missing, p21 is not produced and the stage is set for uncontrolled cell division and the development of cancer. Researchers have also recently determined the structure of the portion of p53 responsible for tumor suppression. This knowledge may provide a basis for the development of therapies to suppress tumor growth or drugs that restore tumor suppressor activity in patients with cancer.

PROGRESS IN TREATING AND PREVENTING CARDIOVASCULAR DISEASES

- **Hormone Replacement Therapy Reduces Heart Disease Risk Factors.** The first major clinical trial to examine the effects of sex hormones on heart disease risk factors in postmenopausal women found that certain hormonal regimens produced significant increases in levels of HDL ("good") cholesterol. For women, a high level of HDL is believed to provide strong protection against coronary heart disease. Estrogen taken alone and estrogen combined with natural progesterone yielded the greatest increases in HDL. The study also found that all of the active treatments tested caused significant decreases in LDL ("bad") cholesterol and fibrinogen, a blood clotting factor predictive of stroke and heart attack. Further, neither estrogen taken alone nor estrogen/progestin combinations increased blood pressure, as had been previously believed. The results also indicated that combination hormonal therapy may be the preferred treatment for women who have a uterus. These study results provide scientifically based guidance for postmenopausal women and their physicians seeking safe hormonal regimens that will improve their heart disease risk factors.

- **Early Surgery Reduces Risk of Stroke by Half.** Many strokes arise from narrowing of the carotid arteries in the neck, which reduces blood supply to the brain. A previous study demonstrated clear benefit from surgery to re-open narrowed carotid arteries in patients with severe blockage (70-99 percent) who had already experienced stroke symptoms. Now, a major trial has just been completed that shows the surgery also benefits patients with a high degree of carotid artery blockage (greater than 60 percent) who have not yet experienced warning symptoms of stroke. The results suggest that, without the surgery, approximately 10 percent of patients with severe carotid narrowing will have a stroke within 5 years, compared to a stroke rate of 5 percent over 5 years with the surgery (which requires accurate determination of the degree of blockage and a skilled surgeon). The study also showed that the benefit of surgery is greater for men than for women.

- **First Risk Factor for Thrombosis Identified.** Thrombosis–the formation of a blood clot within a vessel–can cause major health problems, including the precipitation of heart attack, a form of stroke, and pulmonary embolism, as well as serious systemic conditions like deep vein thrombosis. Women and certain other groups are especially prone to thrombosis, but development of preventive measures has been hindered by the lack of a clear molecular defect or risk factor. Now, investigators have discovered a genetic defect in a blood clotting factor that results in excessive, uncontrolled clotting. This defect is the likely cause of hereditary venous thromboembolism. Researchers have developed a simple test to detect the abnormality, an important step towards treatment and prevention of this common, life-threatening condition.

- **Angioplasty Is a Viable Alternative To Bypass Surgery.** Results are in from the first randomized clinical trial in the U.S. to compare two procedures for treating advanced coronary artery disease. The study demonstrated that patients who receive balloon angioplasty–a procedure that widens diseased arteries by inflation of a balloon-tipped catheter–experience no more deaths, heart attacks, or ischemia (reduced blood flow to the heart) than similar patients who receive coronary artery bypass surgery. Thus, angioplasty is a viable alternative to bypass surgery in selected patients who require revascularization. The economic implications of these results are significant. In the U.S., approximately 309,000 persons underwent bypass surgery and 361,000 had angioplasty in 1992. Although a major limitation of angioplasty is that coronary artery blockage recurs in approximately one third of patients within 3-6 months, the procedure is much less invasive and costly than bypass graft surgery. Data from 1987 estimated the approximate costs of a bypass surgery at $23,417 compared to $9,126 for angioplasty.

INCREASING KNOWLEDGE OF HIV/AIDS AND TREATMENT OF AIDS-RELATED DISEASES

- **AZT Reduces Mother-to-Child HIV Transmission.** The transmission of HIV from infected pregnant women to their newborn offspring is the principal source of pediatric HIV/AIDS worldwide. Annually in the U.S., approximately 7,000 infants are born to HIV+ mothers, with as many as 2,000 of them infected with HIV. Investigators sought to reduce this transmission by giving Zidovudine (AZT) to HIV-infected women during their pregnancy and delivery, and to their offspring for six weeks following delivery. With these treatments, the transmission rate of HIV from mother-to-child was reduced by approximately 67 percent. This therapy could potentially prevent HIV infection in up to 1,300 children per year.

- **Inhibiting Replication of the AIDS Virus (HIV-1).** Scientists have discovered a factor from saliva that inhibits replication of the AIDS virus in the test tube. Their search was based on two observations: HIV-1 is virtually never transmitted orally and the fact that saliva has some antiviral properties. The investigators found that if saliva was added to a dish of cells as they were being infected with HIV-1, viral replication was subsequently inhibited for several weeks. In the next step, they identified the specific component in saliva responsible for this effect–a novel antiviral factor they called Secretory Leukocyte Protease Inhibitor (SLPI). Their studies further suggested that SLPI works by conferring resistance to infection on the host cell, rather than by affecting the virus itself. Identification of the cellular target of SLPI and its mechanism of action may lead to clinical trials with this natural antiviral agent or to the development of strategies for gene therapy in HIV-1 susceptible cells.

- **Protein Boosts Ability to Fight Infections Common in HIV+ Persons.** Non-tuberculous mycobacteria can cause serious life-threatening diseases such as disseminated *Mycobacterium avium* complex, which affects up to 40 percent of people infected with HIV. Researchers have shown that interferon gamma–a protein made by immune system cells to fight infections–produced dramatic clinical benefits in patients with these types of infections. Because their infections were caused by drug resistant strains of bacteria, the patients did not respond to conventional therapies, which were administered for at least 4 months. After treatment with interferon gamma, all patients rapidly improved and many of their symptoms abated. These studies hold promise for treatment of mycobacterial infections, including TB.

- **Eye Implant to Treat Sight-Threatening Infection in AIDS Patients.** Cytomegalovirus (CMV) retinitis is the leading cause of visual loss among AIDS patients, affecting as many as 20-30 percent. Two drugs, ganciclovir and foscarnet, are available for treatment, but they require daily injections, are associated with serious adverse effects, and relapse is common. Investigators have just completed a clinical trial evaluating the safety and efficacy of a ganciclovir-releasing eye implant to treat newly diagnosed CMV retinitis. The experimental device is surgically implanted into the eye and slowly releases the anti-viral drug over a period of several months. The results showed the device halted the progression of CMV retinitis for about eight months, compared to a 15 day time period before the infection worsened in the absence of the implant. This experimental device should improve the treatment, and potentially the quality of life, of AIDS patients with CMV retinitis.

- **A Model and Possible Therapy for AIDS-Related Lymphomas.** A specially bred mouse with a nonfunctional immune system is proving a useful model to study disease development and potential therapies for people with AIDS. The immunodeficient mice were engrafted with human cells that had been infected with the Epstein-Barr virus (EBV), a virus that can induce lymphomas. In this way, researchers created an important model system for the study of lymphomas that arise in people with AIDS. They found that when the mice were treated with a low dose of interleukin-2 (IL-2)--a hormone produced by immune cells to regulate the body's immune response to disease--the occurrence of fatal EBV+ lymphoma was prevented. Investigators are now testing this approach as an innovative strategy in AIDS-related lymphomas in humans. Results from a pilot study have been promising. Post-chemotherapy low-dose IL-2 can prevent or forestall relapse or disease progression for at least 1 year to more than 4.5 years in the majority of such patients, even for those with the most severe immune suppression. These exciting laboratory and clinical observations in AIDS-related lymphomas provide the foundation for an upcoming national clinical trial to define the impact of daily, post-chemotherapy, low-dose IL-2 on various parameters of the disease.

- **New Target for Anti-HIV Drug Development.** Researchers are focusing on p7, a protein of the AIDS virus, as a possible target for drugs to treat HIV infection. Their rationale is that since p7 plays an essential role in the formation of HIV viral particles, a drug that interferes with the function of p7 might prevent HIV-1 replication. In a drug screening assay using cells infected with HIV, scientists identified a potent inhibitor of HIV replication that works by disrupting the function of p7. This new compound may provide important insight into viral replication and will be further tested as a potential therapeutic agent.

- **Long-term Survivors of HIV-1 Infection May Provide Clues for Treatment**. Scientists are hoping to gain insight into the control of HIV-1 by studying a small subset of HIV+ individuals who have survived for more than 10 years with no impairment of their immune system and no evidence of disease. These individuals show intact lymph node architecture and have very low levels of the virus. Some appear to have been infected with a virus that has little or no ability to cause disease. Others have immune system cells that markedly inhibit the HIV-1 infection process, a likely critical element of their immunity. These observations suggest that it is possible for the body to mount an immune response that, although it does not eliminate HIV-1, protects against the induction of disease. Further analysis of these individuals may lead to strategies for inducing such protective immunity in others.

- **Anti-HIV Drugs Yield Critical Information About Virus Production and Destruction.** Investigators have used a class of drugs that inhibit crucial enzymes involved in HIV-1 replication to learn about the dynamics of HIV-1 production and destruction in infected individuals. Treatment with the drugs, known as protease inhibitors, rapidly reduced the amount of virus in the plasma and was accompanied by an increase in circulating CD4 immune cells. Because the production of new virus was blocked, scientists were able to determine the rate at which existing viral particles and CD4 immune cells were destroyed. They also calculated that approximately 1 billion HIV are produced each day, most of which are destroyed within days, and that drug-resistant virus emerge very quickly, within a week of treatment. This information will be critical in designing strategies for the control of HIV-1.

For example, it suggests that multi-drug combinations may offer the best hope for long-term control of HIV replication.

- **Structure of HIV-1 Protein May Aid Design of Anti-HIV Drugs.** Researchers are focusing on the major HIV-1 enzymes as potential targets for drug discovery and development. One of the enzymes, integrase, plays an important role in the insertion of HIV genetic material into host chromosomes. A lack of knowledge about the structure of integrase has impeded scientists in identifying compounds that might inhibit its activity. Now investigators have solved the three-dimensional structure of integrase and have gained important information about essential portions of the enzyme. Other researchers have identified a protein that binds to integrase and stimulates its activity. This knowledge should be valuable in efforts to develop a new class of anti-HIV agents for use in combination with drugs that target other aspects of HIV.

DISEASE MODELS FOR DEVELOPING PREVENTIVE AND THERAPEUTIC STRATEGIES

The development of a model system of a disease is a significant advance for researchers. A model provides a powerful tool for investigators to learn about the mechanism of a disease within the context of a complex living system. This knowledge can lead to the development of methods to detect and diagnose disease, as well as potential therapeutic and preventive strategies.

- **Mouse Model for Obesity Leads to Discovery of Obesity Gene.** In perhaps the greatest discovery in obesity research to date, researchers have isolated a defective mouse gene that results in profound obesity and non-insulin-dependent diabetes mellitus. The scientists located the gene by studying a strain of mouse that can weigh up to five times more than normal. Their studies suggest a mechanism for how the obesity gene controls the amount of fat deposition. The normal mouse gene appears to be switched on in fat tissue, where it generates a protein that is secreted into the bloodstream and, once it reaches the appetite-controlling area of the brain, acts to regulate food intake. A defective obesity gene may produce little or no protein, and so the brain would not receive the proper message about the status of body fat stores, and appetite control would be lost. Investigators used their knowledge of the mouse gene to pinpoint a nearly identical obesity gene in human DNA. Because of the close similarity between the human and mouse genes, it is likely that they perform similar functions. Scientists are now investigating whether the gene is mutated in obese humans. It is likely that human obesity will be much more complicated than obesity in the mouse, possibly involving multiple genes and proteins. Nonetheless, this landmark research may eventually lead to more effective medical therapies for weight problems, and to testing for genetic predisposition for obesity early in life, when dietary modification might help prevent obesity and reduce the prevalence of many chronic obesity-related diseases, including non-insulin-dependent diabetes.

- **First Useful Model of Inflammatory Bowel Disease.** Inflammatory bowel disease (IBD) is a chronic disorder affecting the small and/or large intestine. IBD affects 45-55 people per 100,000 each year in the U.S. Progress in understanding the development of this disease has been hampered by a lack of animal models of the disease. Researchers have recently shown that mice with mutations in specific genes involved in the immune response develop a disease that resembles human IBD, including ulcerative colitis with chronic diarrhea and wasting. These animal models of human IBD will be extremely valuable in studying the immunologic mechanisms that lead to disease and in trials of therapeutic agents.

- **Model for Lou Gehrig's Disease.** People with amyotrophic lateral sclerosis (ALS) have difficulty moving their arms and legs, speaking, and swallowing because cells in the brain and spinal cord that control voluntary muscle movement degenerate, and the muscles normally under their control then waste away. The degeneration is progressive and eventually is fatal. Approximately 10 percent of ALS cases are hereditary and are known to be associated with a defect in a gene for superoxide dismutase (SOD), an enzyme that catalyzes the breakdown of toxic free radicals to oxygen and water. The free radicals broken down by SOD can injure nerve cells and have been implicated in several neurological disorders. Scientists have succeeded in producing mice that contain a human mutant SOD gene. These mice develop limb weakness, impaired gait, limb tremor and paralysis–similar to findings in ALS patients. Establishment of this experimental animal model is considered a major breakthrough in the advancement of research on ALS.

- **Gene Replacement Prevents Lupus-Like Disease in Mice.** Lupus is a chronic autoimmune disorder in which the body's immune system attacks the connective tissue, causing inflammation. Lupus affects nine times as many women as men, with the highest incidence among blacks in the U.S., Chinese in the Far East, and West Indians. An exciting new avenue of research indicates that lupus may involve defects in a process known as apoptosis, or programmed cell death. The body normally eliminates unnecessary, damaged, or potentially harmful cells through apoptosis. In the immune system, apoptosis is responsible for eliminating cells with the potential to react against the body's own tissues. If the process of apoptosis is defective, these self-reactive cells will survive and may cause autoimmune diseases such as lupus. Investigators have recently shown that a strain of mice which develop a lupus-like illness have a defect in a gene that controls apoptosis. When they replaced the defective gene with a normal gene, the mice no longer developed signs of lupus. Better understanding of the role of apoptosis may lead to new treatments targeted to specific defects in lupus.

- **Antibiotic is Effective Treatment in Model of Osteoarthritis.** Affecting approximately 16 million Americans, osteoarthritis (OA) is the most common joint disease and cause of chronic disability in the U.S. The standard treatment is nonsteroidal anti-inflammatory drugs (NSAIDs), but their gastrointestinal side effects are of increasing concern. Elderly women, in whom OA is especially common, incur the greatest morbidity and mortality from complications of NSAID use. Scientists are investigating several non-NSAIDs that show promise for preventing or controlling progression of OA. They have shown that prophylactic oral administration of the antibiotic doxycycline reduces the severity of cartilage damage in an animal model of OA. If doxycycline proves to be as efficacious in patients with OA, it could markedly improve the health of a large segment of our elderly population.

- **Sea Squirt Is Useful Model for Kidney Stones.** Recent studies of stone formation and metabolism in the inch-long sea squirt may help scientists understand kidney stone disease and treatment. Although the marine animal's renal sac bears little physical resemblance to the human kidney, it shares important functional similarity, including stone formation. Researchers have found that the sea squirt carries within its renal sac a microorganism, *Nephromyces,* that breaks down the stones. While they initially thought that enzymes within *Nephromyces* were used to destroy the stones; now it appears that an unnamed bacteria living inside *Nephromyces* may be responsible. Further studies of this model system may provide valuable knowledge about kidney disease and aid in the development of treatments.

- **"Knockout Mouse" to Study Environmental Estrogens.** Many environmental compounds can affect the body similar to the natural hormone, estrogen. Such environmental estrogens include many of the chlorinated pesticides such as DDT and kepone, polychlorinated biphenyls (PCBs), and natural plant products in our diet. They compete with natural estrogen for binding to cells and can affect body processes which are normally controlled by estrogen, including development of secondary sexual characteristics, and growth and maturation of long bones. Environmental estrogens may play a role in a wide range of diseases, such as endometriosis, uterine fibroids, and cancers of the breast, uterus and ovaries. Scientists have recently engineered a transgenic mouse that can aid in defining the role of environmental estrogens in human diseases and dysfunctions. To create this animal model, they "knocked out" an important estrogen receptor gene in the mouse. This allows investigators to evaluate the mechanism of action of hormonally active environmental compounds. The mouse model will be used to study actions of estrogenic chemicals in a variety of organ systems.

VACCINES

A vaccine works by sensitizing the body's immune system to a particular disease-causing bacteria, virus, toxin, or a component of a pathogenic organism. When the infectious agent subsequently invades the body, the immune system recognizes it and mounts an immediate and robust response to destroy the invader before it can cause disease. The many successes of traditional vaccines are well known, but other serious and fatal diseases still have proven stubbornly resistant to vaccines, demanding new approaches. Because the effectiveness and duration of protection of existing vaccines can vary greatly, researchers also try to develop improved versions of some current vaccines.

- **New Whooping Cough Vaccine Highly Effective and Safe.** Whooping cough (pertussis) is a serious respiratory infection that affects infants and young children. The vaccine for whooping cough currently used in the U.S. is not completely effective and is associated with significant and potentially dangerous side effects. Researchers have developed a new vaccine and tested it in the midst of a severe whooping cough epidemic in Sweden. In the trial, the first of its kind, only 4 percent of vaccinated children became infected, compared to 14 percent of non-vaccinated children. In addition to being highly effective, the new vaccine produced far fewer side effects than did the standard vaccine.

- **New and Effective Typhoid vaccine.** Typhoid fever is an infectious disease contracted by eating food or drinking water contaminated with a type of Salmonella bacteria. While typhoid is uncommon in the U.S., epidemics occur regularly in developing countries, and travelers are at risk. Currently available typhoid vaccines require either multiple doses or injections, are accompanied by adverse effects, and provide incomplete protection. Investigators have developed a new vaccine for preventing typhoid fever. In a clinical trial in Nepal, the new vaccine had an effectiveness rate of 74 percent. It requires only a single injection and side effects are rare and minor. It was licensed by the FDA under the trade name Typhium Vi.

- **Potential for a Human Hepatitis E Vaccine.** Hepatitis E is a viral infection spread principally through contaminated water in areas of poor sanitation. Epidemics involving 10,000 to more than 100,000 cases have been reported in Asia and Africa, with mortality rates among pregnant women as high as 20 percent. Scientists have developed a vaccine using a genetically engineered hepatitis E virus that, in animal studies, provided complete protection against hepatitis E disease and partial protection against infection. The vaccine also greatly decreased the amount of virus shed in the feces, a common route of contamination, and completely protected against liver cell damage. These results are promising for development of a hepatitis E vaccine for humans.

- **Promising Candidates for a Melanoma Vaccine.** An important step in developing cancer vaccines is to identify cancer-specific genes or proteins that will be recognized by cells of the immune system (T cells). Researchers have recently identified, cloned, and sequenced genes for 3 melanoma proteins that are recognized by specialized T cells that destroy cancer cells. These findings may prove useful for developing vaccines to boost the body's immune response against tumors. Two of the proteins elicited clinically significant antitumor responses. The third protein is an especially attractive vaccine candidate because it is expressed in essentially all melanomas. A vaccine based on this protein is in preclinical development.

SUBSTANCE ABUSE

- **Effective Medication for Treating Alcoholism.** The development of medication to treat craving presages a new beginning for the treatment of alcoholism. In recent clinical trials, naltrexone–a chemical that neutralizes or impedes the effects of opiates–was very effective in reducing both alcohol craving and consumption. Alcoholics treated with naltrexone experienced fewer days drinking, had less craving for alcohol, a smaller number of relapses, and less alcohol use after relapse. Psychosocial interventions such as supportive therapy and coping skills therapy in combination with naltrexone also proved effective. Naltrexone is awaiting FDA approval as a medication for the treatment of alcoholism. If successful, naltrexone will be the first approved medication for the treatment of alcoholism since antabuse.

- **Novel Opiate Dependence Treatment.** Investigators recently completed a study of the use of buprenorphine for the treatment of opiate dependence. The results indicate that buprenorphine appears both safe and effective in treating opiate dependence across several outcome variables: the number of subjects who were not using heroin (as measured by "clean" urines) increased, the number of subjects retained in treatment rose, and craving for heroin was sharply reduced. A New Drug Application is expected to be filed with the FDA at the end of 1995.

BIOTECHNOLOGY AND BIOENGINEERING

- **A Drug Designed to Switch Genes On and Off.** Scientists have redesigned an immunosuppressant drug into two molecules able to either turn on or turn off the production of a protein in genetically engineered cells. Although this work is still in the early stages, the researchers envision its possible use in a novel form of gene therapy. The therapy would involve removing some of a patient's cells and genetically engineering them to carry genes for both a therapeutic molecule and for a protein to recognize the controller drugs. The engineered cells would be reintroduced into the patients, allowing the production of the therapeutic molecule to be controlled by administration of the "on" or "off" drugs. Eventually, this work may make it possible for someone with diabetes, for example, to simply swallow a drug to turn on modified insulin genes, instead of injecting insulin.

- **Preventing Tissue Damage in Wheelchair Users.** Appropriate seating and positioning are important for maintaining the health of the more than 1.4 million wheelchair users in the U.S. Inadequately designed wheelchairs can lead to poor posture, eventual orthopedic deformity, and serious tissue destruction. To prevent or reduce these major health problems, researchers have developed a method to produce customized contoured seats with easily adjustable back support. The customized wheelchairs reduce the risk of skin and orthopedic conditions associated with poor seating by optimally distributing weight around the soft tissue of the buttocks, preventing soft tissue damage and improving postural control.

- **New Cochlear Implant Component Improves Speech Recognition.** Cochlear implants are neural auditory prosthetic devices that deliver electrical stimulation to the eighth cranial nerve. An essential component of the implant system is the speech processor, which converts speech into patterns of electrical stimulation for the implanted electrodes. Scientists have developed a new type of speech processor that has produced remarkable improvement in the ability of a broad range of implant patients to recognize speech. This technology is now available to many patients with different commercial implant systems.

M:\96INCRE

DHHS–National Institutes of Health
Summary of Targeted Increases
Non–AIDS
(Dollars in thousands)

						FY 1996
ICD	+$2.1M TB	+$4.5 M Women's Health Office	+$8.3 M HPCC	+$49.1 M * Breast Cancer	+$4.5 M Min Hlth Init.	Targeted Increases
FY 1995 BASE	$50,988	$12,750	$70,595	$377,100	$58,297	$569,730
NCI	160			31,733		$31,893
NHLBI				758		758
NIDR						--
NIDDK				3,495		3,495
NINDS						--
NIAID	1,621					1,621
NIGMS				3,794		3,794
NICHD				958		958
NEI				70		70
NIEHS				3,449		3,449
NIA	10			860		870
NIAMS						--
NIDCD						--
NIMH	10			347		357
NIDA	100					100
NIAAA	5			27		32
NINR	20			296		316
NCRR	43		2,000	1,920		3,963
NCHGR	62			1,372		1,434
FIC	41			5		46
NLM			8,339			8,339
OD		4,500	(2,080)		4,500	6,920
B&F						--
Targeted	2,072	4,500	8,259	49,084	4,500	68,415
TOTAL	53,060	17,250	78,854	426,184	62,797	638,145

* Includes an increase of $10,000 for Breast Cancer Action Plan for a total of $20,000.

NATIONAL INSTITUTES OF HEALTH

FY 1996 Congressional Justification

Summary of Appropriations

Total, NIH

	FY 1994 Actual	FY 1995 Appropriation	FY 1995 Current Estimate	FY 1996 Estimate
NCI	2,077,110,000	2,136,408,000	2,136,408,000	2,219,797,000
NHLBI	1,265,007,000	1,297,032,000	1,297,032,000	1,337,021,000
(Prior to HRSA Transfer)	(1,276,178,000)	(1,312,392,000)	(1,312,392,000)	(1,352,381,000)
(Transfer to HRSA)	(11,171,000)	(15,360,000)	(15,360,000)	(15,360,000)
NIDR	170,346,000	175,213,000	175,213,000	180,650,000
NIDDK	714,529,000	737,026,000	737,026,000	760,533,000
NINDS	632,467,000	652,204,000	652,204,000	672,062,000
NIAID	1,065,769,000	1,096,457,000	1,096,457,000	1,153,372,000
NIGMS	875,511,000	904,925,000	904,925,000	933,809,000
NICHD	552,145,000	568,823,000	568,823,000	586,890,000
NEI	290,841,000	300,590,000	300,590,000	309,818,000
NIEHS	264,249,000	272,733,000	272,733,000	284,883,000
NIA	420,977,000	434,580,000	434,580,000	447,608,000
NIAMS	223,326,000	231,399,000	231,399,000	238,467,000
NIDCD	163,562,000	168,933,000	168,933,000	174,049,000
NIMH	612,939,000	631,275,000	631,275,000	652,136,000
NIDA	425,001,000	437,443,000	437,443,000	452,069,000
NIAAA	184,700,000	190,067,000	190,067,000	195,847,000
NINR	51,018,000	52,757,000	52,757,000	55,055,000
NCRR	331,915,000	359,367,000	358,367,000	384,914,000
NCHGR	127,112,000	152,866,000	152,866,000	167,678,000
FIC	21,677,000	23,775,000	23,775,000	24,961,000
Subtotal	10,470,201,000	10,823,873,000	10,822,873,000	11,231,619,000
NLM	118,019,000	128,694,000	128,694,000	139,473,000
OD	227,223,000	239,859,000	239,859,000	257,854,000
B&F	111,039,000	114,120,000	114,120,000	144,120,000
Total , NIH Prior to	10,937,653,000	11,321,906,000	11,320,906,000	11,788,426,000
HRSA Transfer	(11,171,000)	(15,360,000)	(15,360,000)	(15,360,000)
TOTAL, NIH	10,926,482,000	11,306,546,000	11,305,546,000	11,773,066,000

FY 1994 excludes an emergency supplemental of $1,000,000 transferred from the OASH to NCRR for earthquake relief. FY 1995 Current Estimate lowered in the amount of $1,000,000 to reflect the proposed rescisssion in NCRR. All years reflect a transfer to HRSA for the National Marrow Donor Program.

DHHS-National Institutes of Health

Summary of Appropriations

(dollars in thousands)

	FY 1994 Comparable			FY 1995 Estimate			FY 1996 Estimate			Percent Change 96/95		
	ICD Actual	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS
NCI	$1,864,093	$213,017	$2,077,110	$1,917,904	$218,504	$2,136,408	$1,994,007	$225,790	$2,219,797	3.97	3.33	3.90
NHLBI	1,210,030	54,977	1,265,007	1,241,547	55,485	1,297,032	1,279,096	57,925	1,337,021	3.02	4.40	3.08
(Prior to HRSA Transfer)	(1,221,201)	(54,977)	(1,276,178)	(1,256,907)	(55,485)	(1,312,392)	(1,294,456)	(57,925)	(1,352,381)	2.99	4.40	3.05
(Transfer to HRSA)	(11,171)		(11,171)	(15,360)		(15,360)	(15,360)		(15,360)			
NIDR	158,161	12,185	170,346	163,468	11,745	175,213	168,341	12,309	180,650	2.98	4.80	3.10
NIDDK	704,092	10,437	714,529	726,274	10,752	737,026	748,798	11,735	760,533	3.10	9.14	3.19
NINDS	610,354	22,113	632,467	629,463	22,741	652,204	648,255	23,807	672,062	2.99	4.69	3.04
NIAID	522,857	542,912	1,065,769	538,046	558,411	1,096,457	557,354	596,018	1,153,372	3.59	6.73	5.19
NIGMS	851,568	23,943	875,511	880,261	24,664	904,925	907,674	26,135	933,809	3.11	5.96	3.19
NICHD	495,719	56,426	552,145	510,156	58,667	568,823	526,177	60,713	586,890	3.14	3.49	3.18
NEI	282,460	8,381	290,841	291,957	8,633	300,590	300,693	9,125	309,818	2.99	5.70	3.07
NIEHS	258,641	5,608	264,249	266,988	5,745	272,733	278,832	6,051	284,883	4.44	5.33	4.45
NIA	419,291	1,686	420,977	432,865	1,715	434,580	445,823	1,785	447,608	2.99	4.08	3.00
NIAMS	221,825	1,501	223,326	228,520	2,879	231,399	235,428	3,039	238,467	3.02	5.56	3.05
NIDCD	162,713	849	163,562	167,381	1,552	168,933	172,399	1,650	174,049	3.00	6.31	3.03
NIMH	525,757	87,182	612,939	541,840	89,435	631,275	558,580	93,556	652,136	3.09	4.61	3.30
NIDA	281,625	143,376	425,001	290,041	147,402	437,443	298,738	153,331	452,069	3.00	4.02	3.34
NIAAA	175,243	9,457	184,700	180,326	9,741	190,067	185,712	10,135	195,847	2.99	4.04	3.04
NINR	46,789	4,229	51,018	48,180	4,577	52,757	50,159	4,896	55,055	4.11	6.97	4.36
NCRR	270,532	61,383	331,915	293,737	64,630	358,367	316,544	68,370	384,914	7.76	5.79	7.41
NCHGR	126,475	637	127,112	151,866	1,000	152,866	166,678	1,000	167,678	9.75	—	9.69
FIC	12,825	8,852	21,677	14,667	9,108	23,775	15,267	9,694	24,961	4.09	6.43	4.99
SUBTOTAL	9,212,221	1,269,151	10,481,372	9,530,847	1,307,386	10,838,233	9,869,915	1,377,064	11,246,979	3.56	5.33	3.77
NLM	115,237	2,782	118,019	125,748	2,946	128,694	136,311	3,162	139,473	8.40	7.33	8.38
OD	202,685	24,538	227,223	214,465	25,394	239,859	230,256	27,598	257,854	7.36	8.68	7.50
Office of AIDS Res.	1,296,471	(1,296,471)	—	1,335,726	(1,335,726)	—	1,407,824	(1,407,824)	—	5.40	—	—
B&F	111,039	—	111,039	114,120	—	114,120	144,120	—	144,120	26.29	—	26.29
TOTAL, NIH Prior to HRSA Transfer	10,937,653	0	10,937,653	11,320,906	0	11,320,906	11,788,426	0	11,788,426	4.13	—	4.13
Transfer to HRSA	(11,171)		(11,171)	(15,360)		(15,360)	(15,360)		(15,360)			
TOTAL, NIH after HRSA Transfer	**10,926,482**	**0**	**10,926,482**	**11,305,546**	**0**	**11,305,546**	**11,773,066**	**0**	**11,773,066**	**4.14**	**—**	**4.14**

NOTE: FY 1994 excludes an emergency supplemental of $1,000,000 transferred from the OASH to NCRR for earthquake relief. FY 1995 estimate lowered in the amount of $1,000,000 to reflect the proposed rescission in NCRR. All years reflect a transfer to HRSA for The National Marrow Donor Program.

NATIONAL INSTITUTES OF HEALTH
1996 Congressional Justification
Summary by Mechanism

INCLUDES AIDS

	FY 1994 Actual		FY 1995 Appropriation		FY 1995 Current Estimate		FY 1996 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Noncompeting	17602	$4,368,423,000	17284	$4,432,833,000	17284	$4,432,833,000	17628	$4,681,750,000
Admin. supp.	(1147)	50,785,000	(907)	40,873,000	(907)	40,873,000	(818)	39,731,000
Competing	6474	1,456,526,000	6568	1,527,125,000	6568	1,527,125,000	6046	1,507,179,000
Subtotal, RPGs	24076	5,875,734,000	23852	6,000,831,000	23852	6,000,831,000	23874	6,228,660,000
SBIR/STTR	914	126,191,000	1042	172,192,000	1042	172,192,000	1195	194,087,000
Subtotal, RPGs	24990	6,001,925,000	24894	6,173,023,000	24894	6,173,023,000	25069	6,422,747,000
Success Rate		*25%*		*24%*		*24%*		*23%*
Research Ctrs:								
Spec/comp	646	714,505,000	669	746,304,000	669	746,304,000	666	755,919,000
GCRC	76	131,077,000	76	136,640,000	76	136,640,000	76	142,495,000
Biotech.	62	44,832,000	62	46,022,000	62	46,022,000	62	48,542,000
CM/BMM	41	56,968,000	41	57,435,000	41	57,435,000	41	57,515,000
RCMI	19	26,713,000	19	28,802,000	19	28,802,000	19	29,249,000
Subtotal, Centers	844	974,095,000	867	1,015,203,000	867	1,015,203,000	864	1,033,720,000
Other Research:								
Careers	2106	176,590,000	2147	185,828,000	2147	185,828,000	2159	192,012,000
Clin. Ed.	75	8,183,000	73	7,904,000	73	7,904,000	78	8,662,000
Coop. Cl.	417	162,242,000	502	167,421,000	502	167,421,000	533	175,628,000
BRS	107	17,819,000	108	16,753,000	108	16,753,000	160	26,914,000
MBRS	99	46,459,000	103	50,058,000	103	50,058,000	103	51,555,000
Other	834	86,498,000	903	85,720,000	903	85,720,000	936	88,585,000
Subtotal, Other	3638	497,791,000	3836	513,684,000	3836	513,684,000	3969	543,356,000
Total Res. Grants	29472	7,473,811,000	29597	7,701,910,000	29597	7,701,910,000	29902	7,999,823,000
Training								
Individual	2401	60,324,000	2413	62,395,000	2413	62,395,000	2359	63,253,000
Institutional	12305	312,374,000	12241	318,898,000	12241	318,898,000	12182	327,637,000
Total Training	14706	372,698,000	14654	381,293,000	14654	381,293,000	14541	390,890,000
R & D Contracts	1270	754,626,000	1290	777,176,000	1290	777,176,000	1270	802,793,000
(SBIR/STTR)	(60)	(7,409,000)	(52)	(9,715,000)	(52)	(9,715,000)	(56)	(10,190,000)
Intramural Research		1,201,310,000		1,234,644,000		1,234,644,000		1,272,019,000
Res. Mgmt and Support		498,817,000		508,467,000		508,467,000		520,824,000
Cancer Control		145,600,000		192,383,000		192,383,000		222,270,000
Construction		23,339,000		28,000,000		27,000,000		23,000,000
Total, ICDs		10,470,201,000		10,823,873,000		10,822,873,000		11,231,619,000
Library of Medicine		118,019,000		128,694,000		128,694,000		139,473,000
Office of the Director		227,223,000		239,859,000		239,859,000		257,854,000
Buildings and Facilities		111,039,000		114,120,000		114,120,000		144,120,000
Total, NIH		10,926,482,000		11,306,546,000		11,305,546,000		11,773,066,000
Clinical Trials		(1,130,317,000)		(1,167,724,000)		(1,167,724,000)		(1,201,185,000)

NOTE: FY 1994 excludes an emergency supplemental of $1,000,000 transferred from the OASH to NCRR for earthquake relief. FY 1995 Current Estimate lowered in the amount of $1,000,000 to reflect the proposed rescission in NCRR. All years reflect a transfer to HRSA for the National Marrow Donor Program.

NATIONAL INSTITUTES OF HEALTH
1996 Congressional Justification
Summary by Mechanism

EXCLUDES AIDS

	FY 1994 Actual		FY 1995 Appropriation		FY 1995 Current Estimate		FY 1996 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Noncompeting	16538	$3,973,025,000	16044	$3,982,546,000	16044	$3,982,546,000	16511	$4,224,196,000
Admin. supp.	(1083)	46,109,000	(867)	36,759,000	(867)	36,759,000	(778)	35,451,000
Competing	5878	1,295,809,000	6085	1,396,080,000	6085	1,396,080,000	5615	1,343,362,000
Subtotal, RPGs	22416	5,314,943,000	22129	5,415,385,000	22129	5,415,385,000	22126	5,603,009,000
SBIR/STTR	870	119,412,000	951	158,169,000	951	158,169,000	1094	176,636,000
Subtotal, RPGs	23286	5,434,355,000	23080	5,573,554,000	23080	5,573,554,000	23220	5,779,645,000
Success Rate		*25%*		*24%*		*24%*		*22%*
Research Ctrs:								
Spec/comp	613	662,698,000	635	689,900,000	635	689,900,000	632	698,362,000
GCRC	76	101,392,000	76	104,979,000	76	104,979,000	76	108,834,000
Biotech.	62	43,978,000	62	45,168,000	62	45,168,000	62	46,688,000
CM/BMM	30	34,722,000	30	34,580,000	30	34,580,000	30	34,580,000
RCMI	19	21,174,000	19	22,565,000	19	22,565,000	19	22,577,000
Subtotal, Centers	800	863,964,000	822	897,192,000	822	897,192,000	819	911,041,000
Other Research:								
Careers	1987	166,374,000	2024	175,227,000	2024	175,227,000	2033	180,574,000
Clin. Ed.	75	8,183,000	73	7,904,000	73	7,904,000	78	8,662,000
Coop. Cl.	402	148,365,000	487	152,278,000	487	152,278,000	518	160,185,000
BRS	106	17,160,000	108	16,094,000	108	16,094,000	160	25,255,000
MBRS	99	46,043,000	103	49,630,000	103	49,630,000	103	51,098,000
Other	759	71,954,000	836	70,994,000	836	70,994,000	869	73,498,000
Subtotal, Other	3428	458,079,000	3631	472,127,000	3631	472,127,000	3761	499,272,000
Total Res. Grants	27514	6,756,398,000	27533	6,942,873,000	27533	6,942,873,000	27800	7,189,958,000
Training								
Individual	2315	58,266,000	2322	60,100,000	2322	60,100,000	2265	60,852,000
Institutional	11634	294,836,000	11576	301,192,000	11576	301,192,000	11513	309,534,000
Total Training	13949	353,102,000	13898	361,292,000	13898	361,292,000	13778	370,386,000
R & D Contracts	985	474,842,000	996	499,859,000	996	499,859,000	980	513,913,000
(SBIR/STTR)	(56)	(7,126,000)	(51)	(8,949,000)	(51)	(8,949,000)	(52)	(9,508,000)
Intramural Research		1,006,500,000		1,042,465,000		1,042,465,000		1,074,536,000
Res. Mgmt and Support		441,269,000		449,615,000		449,615,000		460,492,000
Cancer Control		145,600,000		192,383,000		192,383,000		222,270,000
Construction		23,339,000		28,000,000		27,000,000		23,000,000
Total, ICDs		9,201,050,000		9,516,487,000		9,515,487,000		9,854,555,000
Library of Medicine		115,237,000		125,748,000		125,748,000		136,311,000
Office of the Director		202,685,000		214,465,000		214,465,000		230,256,000
Buildings and Facilities		111,039,000		114,120,000		114,120,000		144,120,000
Total, NIH		9,630,011,000		9,970,820,000		9,969,820,000		10,365,242,000
Clinical Trials		(771,507,000)		(798,448,000)		(798,448,000)		(824,713,000)

NOTE: FY 1994 excludes an emergency supplemental of $1,000,000 transferred from the OASH to NCRR for earthquake relief. FY 1995 Current Estimate lowered in the amount of $1,000,000 to reflect the proposed rescission in NCRR. All years reflect a transfer to HRSA for the National Marrow Donor Program.

NATIONAL INSTITUTES OF HEALTH

1996 Congressional Justification

Summary by Mechanism

AIDS ONLY

	FY 1994 Actual		FY 1995 Appropriation		FY 1995 Current Estimate		FY 1996 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No	Amount
Noncompeting	1064	$395,398,000	1240	$450,287,000	1240	$450,287,000	1317	$457,554,000
Admin. supp.	(64)	4,676,000	(40)	4,114,000	(40)	4,114,000	(40)	4,280,000
Competing	596	160,717,000	483	131,045,000	483	131,045,000	431	163,817,000
Subtotal, RPGs	1660	560,791,000	1723	585,446,000	1723	585,446,000	1748	625,651,000
SBIR/STTR	44	6,779,000	91	14,023,000	91	14,023,000	101	17,451,000
Subtotal, RPGs	1704	567,570,000	1814	599,469,000	1814	599,469,000	1849	643,102,000
Success Rate		*34%*		*32%*		*32%*		*31%*
Research Ctrs:								
Spec/comp	33	51,807,000	34	56,404,000	34	56,404,000	34	57,557,000
GCRC	0	29,685,000	0	31,661,000	0	31,661,000	0	33,661,000
Biotech.	0	854,000	0	854,000	0	854,000	0	1,854,000
CM/BMM	11	22,246,000	11	22,855,000	11	22,855,000	11	22,935,000
RCMI	0	5,539,000	0	6,237,000	0	6,237,000	0	6,672,000
Subtotal, Centers	44	110,131,000	45	118,011,000	45	118,011,000	45	122,679,000
Other Research:								
Careers	119	10,216,000	123	10,601,000	123	10,601,000	126	11,438,000
Clin. Ed.	0	0	0	0	0	0	0	0
Coop. Cl.	15	13,877,000	15	15,143,000	15	15,143,000	15	15,443,000
BRS	1	659,000	0	659,000	0	659,000	0	1,659,000
MBRS	0	416,000	0	428,000	0	428,000	0	457,000
Other	75	14,544,000	67	14,726,000	67	14,726,000	67	15,087,000
Subtotal, Other	210	39,712,000	205	41,557,000	205	41,557,000	208	44,084,000
Total Res. Grants	1958	717,413,000	2064	759,037,000	2064	759,037,000	2102	809,865,000
Training								
Individual	86	2,058,000	91	2,295,000	91	2,295,000	94	2,401,000
Institutional	671	17,538,000	665	17,706,000	665	17,706,000	669	18,103,000
Total Training	757	19,596,000	756	20,001,000	756	20,001,000	763	20,504,000
R & D Contracts	285	279,784,000	294	277,317,000	294	277,317,000	290	288,880,000
(SBIR/STTR)	(4)	(283,000)	(1)	(766,000)	(1)	(766,000)	(4)	(682,000)
Intramural Research		194,810,000		192,179,000		192,179,000		197,483,000
Res. Mgmt and Support		57,548,000		58,852,000		58,852,000		60,332,000
Cancer Control		0		0		0		0
Construction		0		0		0		0
Total, ICDs		1,269,151,000		1,307,386,000		1,307,386,000		1,377,064,000
Library of Medicine		2,782,000		2,946,000		2,946,000		3,162,000
Office of the Director		24,538,000		25,394,000		25,394,000		27,598,000
Buildings and Facilities		0		0		0		0
Total, NIH		1,296,471,000		1,335,726,000		1,335,726,000		1,407,824,000
Clinical Trials		(358,810,000)		(369,276,000)		(369,276,000)		(376,472,000)

DHHS–NATIONAL INSTITUTES OF HEALTH

History of Appropriations

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1981	$3,512,320,000	$3,572,427,000	$3,564,765,000	$3,569,406,000 2/
1982	3,310,985,000 3/	3,834,958,000	3,818,710,000	3,641,875,000 4/
1983	3,748,771,000	4,013,450,000	4,028,591,000	4,023,969,000 5/
1984	4,091,958,000	4,314,501,000 6/	4,322,912,000 6/	4,493,588,000 7/
1985	4,566,453,000	4,834,343,000 8/	5,170,203,000	5,149,459,000
1986	4,852,680,000	5,247,836,000 9/	5,463,658,000	5,498,454,000
1986 Sequester				(236,243,000)
1987	4,936,157,000 10/	6,152,775,000	6,080,875,000	6,182,910,000
1988	8,260,277,000 11/	7,036,285,000 12/	6,408,176,000	6,666,693,000
1989	6,535,207,000 13/	6,862,495,000 14/	7,199,298,000	7,152,207,000 14/
1990	6,776,727,000 16/	7,678,625,000 17/	7,713,064,000 17/	7,672,922,000 18/
1990 Sequester				(96,570,000)
1991	7,929,686,000	8,317,654,000 19/	8,347,085,000	8,276,739,000 20/
1991 Sequester				(107,000)
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 21/
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 22/
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,937,653,000 23/
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,321,906,000 24/
1996	11,773,066,000 25/			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Authority was a Continuing Resolution; reflects a rescission of $47,041,000 under P.L. 97–12.

3/ September budget; original request was $3,762,483,000.

4/ Continuing resolution was the lower of the House or Senate Allowance less a 4% reduction.

5/ Authority was a Continuing Resolution.

6/ Excludes $166,368,000 not considered.

7/ Includes $175,838,000 authorized under a Continuing Resolution.

8/ Includes $237,435,000 for NRSA training, not considered.

9/ Excludes $217,943,000 for NRSA training, not considered.

10/ Reflects transfer of AIDS research activities to OASH. The House allowance consolidated AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation distributed the funds among the Institutes.

11/ Includes proposed advanced appropriation of $2,726,000 for outyear cost of competing RPGs in 1988.

12/ The House allowance consolidated AIDS funding in OASH.

13/ The 1989 request excludes funds for AIDS, proposed for consolidation in OASH.

14/ Excludes $249,464,000 not considered.

15/ Includes real transfer of $7,443,000 to OASH for AZT.

16/ The 1990 request excludes funds for AIDS, proposed for consolidation in OASH.

17/ Includes $752,670,000 for AIDS research.

18/ Reflects reductions of $10,000,000 for extramural salary cap savings, $4,000,000 for procurement reform and a $10,428,000 reduction in salaries & expense.

19/ Excludes $304,814,000 not considered.

20/ Reflects enacted administrative reduction of $29,909,000 for salaries and expense and $205,134,000 associated with the 2.41 percent across the board reduction.

21/ Reflects enacted administrative reduction of $69,603,000 for salaries and expense a travel reduction of $5,984,000, and a rescission of $13,131,000.

22/ Reflects enacted administrative reductions of an across the board .8 percent for $83,571,000, $34,857,000 for salaries and expenses and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.

23/ Reflects a salaries and expense rescission of $18,120,000. Excludes $1,000,000 supplemental in NCRR for earthquake relief.

24/ Includes $1,299,328,000 for HIV Research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of $7,446,000 for procurement, $345,000 for rent and $4,401,000 for bonus pay. Excludes proposed rescission of $1,000,000 in NCRR related to construction.

25/ Includes $1,407,824,000 for HIV Research.

INCLUDES AIDS

NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS BY TOTAL MECHANISM

(Dollars in Thousands)

Mechanism	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Actual	FY 1995 Approp.	FY 1995 Current Est.	FY 1996 Estimate
Research Project Grants	$2,851,558	$3,121,780	$3,729,454	$4,028,722	$4,405,646	$4,625,833	$5,046,134	$5,459,375	$5,655,630	$5,957,244	$6,001,925	$6,173,023	$6,173,023	$6,422,747
Research Centers	596,131	493,660	561,954	615,668	657,767	702,216	796,007	891,772	903,204	973,723	974,095	1,015,203	1,015,203	1,033,720
Other Research	331,983	324,430	374,158	394,980	441,348	493,993	546,136	561,400	547,837	542,705	497,791	513,684	513,684	543,356
Subtotal Research Grant	3,779,672	3,939,870	4,665,566	5,039,370	5,504,761	5,822,041	6,388,277	6,912,547	7,106,671	7,473,672	7,473,811	7,701,910	7,701,910	7,999,823
Research Training	238,465	232,873	256,407	282,941	283,015	318,896	342,260	348,018	350,806	372,696	372,696	381,293	381,293	390,890
R & D Contracts	383,263	358,258	503,586	532,446	583,696	630,487	664,696	705,821	693,506	786,249	754,626	777,178	777,178	802,793
Intramural Research	639,451	640,177	748,637	805,417	882,417	975,671	1,048,834	1,132,166	1,160,950	1,201,091	1,201,310	1,234,644	1,234,644	1,272,019
Res. Mgt. & Support	273,098	256,909	289,925	323,499	356,667	405,358	434,706	484,327	493,200	497,866	498,817	508,467	508,467	520,824
Cancer Control	63,794	61,372	67,457	69,682	74,100	75,433	85,390	107,569	105,293	145,600	145,600	182,383	182,383	222,270
Construction	13,100	9,439	9,550	0	31,345	18,322	7,349	12,000	7,528	23,421	23,339	28,000	27,000	23,000
Subtotal ICDs	5,390,843	5,498,898	6,541,128	7,033,355	7,716,001	8,244,408	8,971,514	9,702,448	9,919,956	10,479,807	10,470,201	10,823,873	10,822,873	11,231,619
Library of Medicine	55,184	55,206	61,675	67,700	78,798	81,683	91,182	102,937	103,498	117,783	118,019	128,694	128,694	139,473
Office of the Director	35,396	114,712	56,917	66,875	74,371	111,729	98,153	143,542	191,935	227,044	227,223	239,859	239,859	257,854
Buildings & Facilities	15,675	19,933	25,786	19,029	24,416	67,436	57,091	61,441	112,731	86,335	111,039	114,120	114,120	144,120
Total, NIH	5,497,098	5,688,749	6,685,506	7,186,959	7,893,586	8,505,256	9,217,940	10,010,368	10,328,117	10,910,969	10,926,482	11,306,546	11,305,546	11,773,066

FY 1994 excludes an emergency supplemental of $1,000,000 transferred from the OASH to NCRR for earthquake relief. FY 1995 Current Estimate lowered in the amount of $1,000,000 to reflect the proposed rescission in NCRR. All years reflect a transfer to HRSA for the National Marrow Donor Program.

NATIONAL INSTITUTES OF HEALTH

PERCENTAGE SHARE OF NIH TOTAL BY MECHANISM

INCLUDES AIDS

Mechanism	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Actual	FY 1995 Approp.	FY 1995 Current Est.	FY 1996 Estimate
Research Project Grants	53.7%	54.9%	55.8%	56.1%	55.8%	54.4%	54.7%	54.5%	54.8%	54.6%	54.9%	54.6%	54.6%	54.6%
Research Centers	9.0%	8.7%	8.4%	8.6%	8.3%	8.3%	8.6%	8.9%	8.7%	8.9%	8.9%	9.0%	9.0%	8.8%
Other Research	6.0%	5.7%	5.6%	5.5%	5.6%	5.8%	5.9%	5.6%	5.3%	5.0%	4.6%	4.5%	4.5%	4.6%
Subtotal Research Grants	68.8%	69.3%	69.8%	70.1%	69.7%	68.5%	69.3%	69.1%	68.8%	68.5%	68.4%	68.1%	68.1%	68.0%
Research Training	4.3%	4.1%	3.8%	3.7%	3.6%	3.7%	3.7%	3.5%	3.4%	3.4%	3.4%	3.4%	3.4%	3.3%
R & D Contracts	7.0%	6.3%	7.5%	7.4%	7.4%	7.4%	7.2%	7.1%	6.7%	7.0%	6.9%	6.9%	6.9%	6.8%
Intramural Research	11.6%	11.3%	11.2%	11.2%	11.2%	11.5%	11.4%	11.3%	11.2%	11.0%	11.0%	10.9%	10.9%	10.8%
Res. Mgt. & Support	5.0%	4.5%	4.3%	4.5%	4.5%	4.8%	4.7%	4.8%	4.8%	4.6%	4.6%	4.5%	4.5%	4.4%
Cancer Control	1.2%	1.1%	1.0%	1.0%	0.9%	0.9%	0.9%	1.1%	1.0%	1.3%	1.3%	1.7%	1.7%	1.9%
Construction	0.2%	0.2%	0.1%	0.0%	0.4%	0.2%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%
Subtotal ICDs	98.1%	96.7%	97.8%	97.9%	97.8%	96.9%	97.3%	96.9%	96.0%	96.0%	95.8%	95.7%	95.7%	95.4%
Library of Medicine	1.0%	1.0%	0.9%	0.9%	1.0%	1.0%	1.0%	1.0%	1.0%	1.1%	1.1%	1.1%	1.1%	1.2%
Office of the Director	0.6%	2.0%	0.9%	0.9%	0.9%	1.3%	1.1%	1.4%	1.9%	2.1%	2.1%	2.1%	2.1%	2.2%
Buildings & Facilities	0.3%	0.4%	0.4%	0.3%	0.3%	0.8%	0.6%	0.6%	1.1%	0.8%	1.0%	1.0%	1.0%	1.2%
Total, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations
FY 1985 - FY 1996
(Dollars in Thousands)

INCLUDES AIDS

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994* Actual	FY 1995 Approp.	FY 1995** Current Est.	FY 1996 Estimate
NCI	$1,177,853	$1,210,284	$1,402,790	$1,468,435	$1,570,342	$1,644,330	$1,712,669	$1,947,571	$1,978,340	$2,077,110	$2,136,406	$2,136,406	$2,219,797
NHLBI	803,810	821,901	929,881	965,283	1,045,508	1,070,683	1,125,915	1,190,070	1,214,693	1,265,007	1,297,032	1,297,032	1,337,021
NIDR	100,414	98,755	117,926	126,216	130,689	135,432	148,691	158,900	161,116	170,346	175,213	175,213	180,650
NIDDK	539,499	436,037	510,880	534,359	559,274	579,964	615,262	661,446	680,514	714,529	737,026	737,026	760,533
NINDS	398,170	414,406	490,136	458,792	471,632	489,348	542,313	580,790	599,466	632,467	652,204	652,204	672,062
NIAID	370,047	367,142	545,433	638,521	740,239	831,181	906,003	980,062	984,114	1,065,769	1,096,457	1,096,457	1,153,372
NIGMS	480,975	493,535	570,867	627,465	682,134	680,305	761,231	814,297	832,191	875,511	904,925	904,925	933,809
NICHD	312,578	308,211	366,651	396,584	425,268	441,955	478,947	518,577	527,767	552,145	568,823	568,823	586,890
NEI	181,298	186,343	216,528	224,835	230,999	236,456	253,354	269,766	275,368	290,841	300,590	300,590	309,818
NIEHS	194,486	188,819	209,251	215,439	223,309	228,725	240,606	251,484	251,047	264,249	272,733	272,733	284,883
NIA	142,968	150,910	177,461	194,548	222,545	238,927	323,791	382,882	399,523	420,977	434,580	434,580	447,608
NIAMS	0	111,336	138,675	147,543	159,886	168,538	193,449	203,516	212,208	223,326	231,399	231,399	238,467
NIDCD	0	0	0	75,691	94,275	117,283	134,957	148,748	154,655	163,562	168,933	168,933	174,049
NIMH	232,734	242,066	287,804	327,514	384,928	440,222	511,967	560,285	582,851	612,939	631,275	631,275	652,136
NIDA	81,130	83,311	139,307	156,252	228,131	329,560	383,656	399,100	403,065	425,001	437,443	437,443	452,069
NIAAA	61,677	66,395	83,357	92,763	120,051	149,194	158,141	171,481	176,128	184,700	190,067	190,067	195,847
NINR	0	16,193	19,924	23,361	29,118	33,508	39,892	44,925	48,477	51,018	52,757	52,757	55,055
NCRR	303,641	292,388	322,781	344,150	381,934	353,771	335,776	314,198	312,635	331,915	359,367	358,367	384,914
NCHGR	0	0	0	0	0	59,527	87,389	104,756	106,095	127,112	152,866	152,866	167,678
FIC	11,563	10,866	11,376	15,604	15,739	15,479	17,505	19,574	19,702	21,677	23,775	23,775	24,961
Subtotal, ICDs	5,390,843	5,496,898	6,541,128	7,033,355	7,716,001	8,244,408	8,971,514	9,702,448	9,919,955	10,470,201	10,823,873	10,822,873	11,231,619
NLM	55,184	55,206	61,675	67,700	78,798	81,683	91,182	102,937	103,496	118,019	128,694	128,694	139,473
OD	35,396	114,712	56,917	66,875	74,371	111,729	98,153	143,542	191,935	227,223	239,859	239,859	257,854
B&F	15,675	19,933	25,786	19,029	24,416	67,436	57,091	61,441	112,731	111,039	114,120	114,120	144,120
TOTAL, NIH	5,497,098	5,688,749	6,685,506	7,186,959	7,893,586	8,505,256	9,217,940	10,010,368	10,328,117	10,926,482	11,306,546	11,305,546	11,773,066

* Excludes an emergency supplemental of $1,000,000 transferred from OASH for earthquake relief.

** Estimate lowered in the amount of $1,000,000 to reflect the proposed rescission in NCRR.

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations
Percent to Total
FY 1985 - FY 1996

INCLUDES AIDS

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Actual	FY 1995 Approp.	FY 1995 Current Est.	FY 1996 Estimate
NCI	21.4%	21.3%	21.0%	20.4%	19.9%	19.3%	18.6%	19.5%	19.2%	19.0%	18.9%	18.9%	18.9%
NHLBI	14.6%	14.4%	13.9%	13.4%	13.2%	12.6%	12.2%	11.9%	11.8%	11.6%	11.5%	11.5%	11.4%
NIDR	1.8%	1.7%	1.8%	1.8%	1.7%	1.6%	1.6%	1.6%	1.6%	1.6%	1.5%	1.5%	1.5%
NIDDK	9.8%	7.7%	7.6%	7.4%	7.1%	6.8%	6.7%	6.6%	6.6%	6.5%	6.5%	6.5%	6.5%
NINDS	7.2%	7.3%	7.3%	6.4%	6.0%	5.8%	5.9%	5.8%	5.8%	5.8%	5.8%	5.8%	5.7%
NIAID	6.7%	6.5%	8.2%	8.9%	9.4%	9.8%	9.8%	9.6%	9.5%	9.8%	9.7%	9.7%	9.8%
NIGMS	8.7%	8.7%	8.5%	8.7%	8.6%	8.0%	8.3%	8.1%	8.1%	8.0%	8.0%	8.0%	7.9%
NICHD	5.7%	5.4%	5.5%	5.5%	5.4%	5.2%	5.2%	5.2%	5.1%	5.1%	5.0%	5.0%	5.0%
NEI	3.3%	3.3%	3.2%	3.1%	2.9%	2.8%	2.7%	2.7%	2.7%	2.7%	2.7%	2.7%	2.6%
NIEHS	3.5%	3.3%	3.1%	3.0%	2.8%	2.7%	2.6%	2.5%	2.4%	2.4%	2.4%	2.4%	2.4%
NIA	2.6%	2.7%	2.7%	2.7%	2.8%	2.8%	3.5%	3.8%	3.9%	3.9%	3.8%	3.8%	3.8%
NIAMS	0.0%	2.0%	2.1%	2.1%	2.0%	2.0%	2.1%	2.0%	2.1%	2.0%	2.0%	2.0%	2.0%
NIDCD	0.0%	0.0%	0.0%	1.1%	1.2%	1.4%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%
NIMH	4.2%	4.3%	4.3%	4.6%	4.9%	5.2%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.5%
NIDA	1.5%	1.5%	2.1%	2.2%	2.9%	3.9%	4.2%	4.0%	3.9%	3.9%	3.9%	3.9%	3.8%
NIAAA	1.1%	1.2%	1.2%	1.3%	1.5%	1.8%	1.7%	1.7%	1.7%	1.7%	1.7%	1.7%	1.7%
NINR	0.0%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%	0.5%
NCRR	5.5%	5.1%	4.8%	4.8%	4.8%	4.2%	3.6%	3.1%	3.0%	3.0%	3.2%	3.2%	3.3%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	0.9%	1.0%	1.0%	1.2%	1.4%	1.4%	1.4%
FIC	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Subtotal, ICDs	98.1%	96.7%	97.8%	97.9%	97.8%	96.9%	97.3%	96.9%	96.0%	95.8%	95.7%	95.7%	95.4%
NLM	1.0%	1.0%	0.9%	0.9%	1.0%	1.0%	1.0%	1.0%	1.0%	1.1%	1.1%	1.1%	1.2%
OD	0.6%	2.0%	0.9%	0.9%	0.9%	1.3%	1.1%	1.4%	1.9%	2.1%	2.1%	2.1%	2.2%
B&F	0.3%	0.4%	0.4%	0.3%	0.3%	0.8%	0.6%	0.6%	1.1%	1.0%	1.0%	1.0%	1.2%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985-1996

EXCLUDES AIDS

(Dollars in Thousands)

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	1993	FY 1994 Actual	FY 1995 Approp.	FY 1995 Current Est	FY 1996 Estimate
NCI	$1,150,979	$1,165,234	$1,339,035	$1,378,491	$1,448,095	$1,494,026	$1,551,800	$1,781,903	$1,805,311	$1,864,093	$1,917,904	$1,917,904	$1,994,007
NHLBI	794,487	806,433	912,737	940,398	1,007,448	1,028,599	1,079,509	1,143,864	1,166,635	1,210,030	1,241,547	1,241,547	1,279,096
NIDR	100,317	97,043	114,679	122,366	126,769	130,770	142,477	150,746	152,741	158,161	163,468	163,468	168,341
NIDDK	539,499	436,037	510,385	531,029	555,717	574,678	608,972	654,274	674,068	704,092	726,274	726,274	748,798
NINDS	395,002	412,971	488,451	446,450	458,563	473,190	525,662	563,198	581,050	610,354	629,463	629,463	648,255
NIAID	346,774	303,866	399,673	415,223	428,962	438,098	475,063	511,292	524,416	522,857	538,046	538,046	557,354
NIGMS	480,975	493,535	565,447	619,741	671,304	665,691	745,643	798,197	815,341	851,568	880,261	880,261	907,674
NICHD	312,578	306,811	361,889	379,431	402,831	415,206	446,338	483,848	488,960	495,719	510,156	510,156	526,177
NEI	181,098	186,247	216,275	221,005	226,171	230,923	247,674	263,864	269,085	282,460	291,957	291,957	300,693
NIEHS	194,486	188,819	209,035	211,543	219,171	224,467	236,092	247,268	246,783	258,641	266,988	266,988	278,832
NIA	142,968	150,910	177,277	194,187	222,102	238,068	322,806	381,810	398,370	419,291	432,865	432,865	445,823
NIAMS	0	111,336	138,575	146,982	159,213	167,300	191,816	201,822	210,448	221,825	228,520	228,520	235,428
NIDCD	0	0	0	75,691	94,275	117,283	134,462	148,265	154,037	162,713	167,381	167,381	172,399
NIMH	230,932	237,006	277,334	296,326	336,555	376,891	439,247	484,145	504,418	525,757	541,840	541,840	558,580
NIDA	80,452	76,382	119,077	122,404	167,307	236,925	260,968	273,831	277,042	281,625	290,041	290,041	298,738
NIAAA	61,677	66,395	80,987	87,970	113,921	141,214	150,145	163,491	169,350	175,243	180,326	180,326	185,712
NINR	0	16,193	19,924	22,759	28,416	32,521	37,347	42,215	45,511	46,789	48,180	48,180	50,159
NCRR	300,839	286,231	311,754	315,867	314,318	307,624	288,347	264,147	261,754	271,532	294,737	293,737	316,544
NCHGR	0	0	0	0	0	59,527	87,389	104,756	106,095	126,475	151,866	151,866	166,678
FIC	11,563	10,866	11,376	11,099	11,120	10,581	12,154	13,981	14,018	12,825	14,667	14,667	15,267
Subtotal, ICDs	5,324,626	5,352,315	6,251,910	6,538,962	6,992,258	7,363,582	7,983,911	8,676,917	8,865,433	9,202,050	9,516,487	9,515,487	9,854,555
NLM	55,184	55,206	61,675	67,700	78,778	81,190	90,663	101,880	102,395	115,237	125,748	125,748	136,311
OD	35,396	114,639	52,158	61,239	61,506	111,729	86,416	128,429	177,354	202,685	214,465	214,465	230,256
B&F	15,675	19,933	25,786	18,659	18,644	54,556	52,125	53,683	108,978	111,039	114,120	114,120	144,120
TOTAL, NIH	5,430,881	5,542,093	6,391,529	6,686,560	7,151,186	7,611,057	8,213,115	8,960,909	9,254,160	9,631,011	9,970,820	9,969,820	10,365,242

NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985-1996

EXCLUDES AIDS

PERCENT TO TOTAL

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	1993	FY 1994 Actual	FY 1995 Approp.	FY 1995 Current Est.	FY 1996 Estimate
NCI	21.2%	21.0%	21.0%	20.6%	20.2%	19.6%	18.9%	19.9%	19.5%	19.4%	19.2%	19.2%	19.2%
NHLBI	14.6%	14.6%	14.3%	14.1%	14.1%	13.5%	13.1%	12.8%	12.6%	12.6%	12.5%	12.5%	12.3%
NIDR	1.8%	1.8%	1.8%	1.8%	1.8%	1.7%	1.7%	1.7%	1.7%	1.6%	1.6%	1.6%	1.6%
NIDDK	9.9%	7.9%	8.0%	7.9%	7.8%	7.6%	7.4%	7.3%	7.3%	7.3%	7.3%	7.3%	7.2%
NINDS	7.3%	7.5%	7.6%	6.7%	6.4%	6.2%	6.4%	6.3%	6.3%	6.3%	6.3%	6.3%	6.3%
NIAID	6.4%	5.5%	6.3%	6.2%	6.0%	5.8%	5.8%	5.7%	5.7%	5.4%	5.4%	5.4%	5.4%
NIGMS	8.9%	8.9%	8.8%	9.3%	9.4%	8.7%	9.1%	8.9%	8.8%	8.8%	8.8%	8.8%	8.8%
NICHD	5.8%	5.5%	5.7%	5.7%	5.6%	5.5%	5.4%	5.4%	5.3%	5.1%	5.1%	5.1%	5.1%
NEI	3.3%	3.4%	3.4%	3.3%	3.2%	3.0%	3.0%	2.9%	2.9%	2.9%	2.9%	2.9%	2.9%
NIEHS	3.6%	3.4%	3.3%	3.2%	3.1%	2.9%	2.9%	2.8%	2.7%	2.7%	2.7%	2.7%	2.7%
NIA	2.6%	2.7%	2.8%	2.9%	3.1%	3.1%	3.9%	4.3%	4.3%	4.4%	4.3%	4.3%	4.3%
NIAMS	0.0%	2.0%	2.2%	2.2%	2.2%	2.2%	2.3%	2.3%	2.3%	2.3%	2.3%	2.3%	2.3%
NIDCD	0.0%	0.0%	0.0%	1.1%	1.3%	1.5%	1.6%	1.7%	1.7%	1.7%	1.7%	1.7%	1.7%
NIMH	4.3%	4.3%	4.3%	4.4%	4.7%	5.0%	5.3%	5.4%	5.5%	5.5%	5.4%	5.4%	5.4%
NIDA	1.5%	1.4%	1.9%	1.8%	2.3%	3.1%	3.2%	3.1%	3.0%	2.9%	2.9%	2.9%	2.9%
NIAAA	1.1%	1.2%	1.3%	1.3%	1.6%	1.9%	1.8%	1.8%	1.8%	1.8%	1.8%	1.8%	1.8%
NINR	0.0%	0.3%	0.3%	0.3%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
NCRR	5.5%	5.2%	4.9%	4.7%	4.4%	4.0%	3.5%	2.9%	2.8%	2.8%	3.0%	2.9%	3.1%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	1.1%	1.2%	1.1%	1.3%	1.5%	1.5%	1.6%
FIC	0.2%	0.2%	0.2%	0.2%	0.2%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%
Subtotal, ICDs	98.0%	96.6%	97.8%	97.8%	97.8%	96.7%	97.2%	96.8%	95.8%	95.5%	95.4%	95.4%	95.1%
NLM	1.0%	1.0%	1.0%	1.0%	1.1%	1.1%	1.1%	1.1%	1.1%	1.2%	1.3%	1.3%	1.3%
OD	0.7%	2.1%	0.8%	0.9%	0.9%	1.5%	1.1%	1.4%	1.9%	2.1%	2.2%	2.2%	2.2%
B&F	0.3%	0.4%	0.4%	0.3%	0.3%	0.7%	0.6%	0.6%	1.2%	1.2%	1.1%	1.1%	1.4%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

AIDS ONLY

NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS
FY 1985 - FY 1996
(Dollars in Thousands)

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Actual	FY 1995 Approp	FY 1996 Estimate
NCI	$26,874	$45,050	$63,755	$89,944	$122,247	$150,304	$160,869	$165,668	$173,029	$213,017	$218,504	$225,790
NHLBI	9,323	15,468	17,244	24,885	38,088	42,056	46,406	46,206	48,058	54,977	55,485	57,925
NIDR	97	1,712	3,247	3,850	3,920	4,662	6,214	8,154	8,375	12,185	11,745	12,309
NIDDK	0	0	495	3,330	3,557	5,306	6,290	7,172	6,446	10,437	10,752	11,735
NINDS	1,168	1,435	3,685	12,342	13,069	16,158	16,651	17,592	18,416	22,113	22,741	23,807
NIAID	23,273	63,276	145,760	223,298	311,277	393,083	430,940	448,940	459,698	542,912	558,411	596,018
NIGMS	0	0	5,420	7,724	10,830	14,614	15,588	16,100	16,850	23,943	24,664	26,135
NICHD	0	1,400	4,762	17,153	22,437	26,749	32,609	34,729	38,807	56,426	58,667	60,713
NEI	200	96	253	3,830	4,828	5,533	5,680	5,902	6,283	8,381	8,633	9,125
NIEHS	0	0	216	3,896	4,138	4,258	4,514	4,216	4,264	5,608	5,745	6,051
NIA	0	0	184	361	443	859	985	1,072	1,153	1,686	1,715	1,785
NIAMS	0	0	100	561	673	1,238	1,633	1,694	1,760	1,501	2,879	3,039
NIDCD	0	0	0	0	0	0	495	483	618	849	1,552	1,650
NIMH	1,802	5,060	10,470	31,188	48,373	63,331	72,720	76,140	78,433	87,182	89,435	93,556
NIDA	678	6,929	20,230	33,848	60,824	92,635	122,688	125,269	126,023	143,376	147,402	153,331
NIAAA	0	0	2,370	4,793	6,130	7,980	7,996	7,990	6,778	9,457	9,741	10,135
NINR	0	0	0	602	702	987	2,545	2,710	2,966	4,229	4,577	4,896
NCRR	2,802	6,157	11,027	28,283	67,616	46,147	47,429	50,051	50,881	61,383	64,630	68,370
NCHGR	0	0	0	0	0	0	0	0	0	637	1,000	1,000
FIC	0	0	0	4,505	4,619	4,898	5,351	5,593	5,684	8,852	9,108	9,694
Subtotal, ICDs	66,217	146,583	289,218	494,393	723,771	880,798	987,603	1,025,681	1,054,522	1,269,151	1,307,386	1,377,064
NLM	0	0	0	0	20	493	519	1,057	1,101	2,782	2,946	3,162
OD	0	73	4,759	5,636	12,865	10,284	11,737	15,113	14,581	24,538	25,394	27,598
B&F	0	0	0	370	5,772	12,880	4,966	7,758	3,753	0	0	0
TOTAL, NIH	66,217	146,656	293,977	500,399	742,428	904,455	1,004,825	1,049,609	1,073,957	1,296,471	1,335,726	1,407,824

NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS
FY 1985 - FY 1996
Percent toTotal

AIDS ONLY

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Actual	FY 1995 Approp.	FY 1996 Estimate
NCI	40.6%	30.7%	21.7%	18.0%	16.5%	16.6%	16.0%	15.8%	16.1%	16.4%	16.4%	16.0%
NHLBI	14.1%	10.5%	5.9%	5.0%	5.1%	4.6%	4.6%	4.4%	4.5%	4.2%	4.2%	4.1%
NIDR	0.1%	1.2%	1.1%	0.8%	0.5%	0.5%	0.6%	0.8%	0.8%	0.9%	0.9%	0.9%
NIDDK	0.0%	0.0%	0.2%	0.7%	0.5%	0.6%	0.6%	0.7%	0.6%	0.8%	0.8%	0.8%
NINDS	1.8%	1.0%	1.3%	2.5%	1.8%	1.8%	1.7%	1.7%	1.7%	1.7%	1.7%	1.7%
NIAID	35.1%	43.1%	49.6%	44.6%	41.9%	43.5%	42.9%	42.8%	42.8%	41.9%	41.8%	42.3%
NIGMS	0.0%	0.0%	1.8%	1.5%	1.5%	1.6%	1.6%	1.5%	1.6%	1.8%	1.8%	1.9%
NICHD	0.0%	1.0%	1.6%	3.4%	3.0%	3.0%	3.2%	3.3%	3.6%	4.4%	4.4%	4.3%
NEI	0.3%	0.1%	0.1%	0.8%	0.7%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%
NIEHS	0.0%	0.0%	0.1%	0.8%	0.6%	0.5%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
NIA	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
NIAMS	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.2%	0.2%
NIDCD	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%
NIMH	2.7%	3.5%	3.6%	6.2%	6.5%	7.0%	7.2%	7.3%	7.3%	6.7%	6.7%	6.6%
NIDA	1.0%	4.7%	6.9%	6.8%	8.2%	10.2%	12.2%	11.9%	11.7%	11.1%	11.0%	10.9%
NIAAA	0.0%	0.0%	0.8%	1.0%	0.8%	0.9%	0.8%	0.8%	0.6%	0.7%	0.7%	0.7%
NINR	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
NCRR	4.2%	4.2%	3.8%	5.7%	9.1%	5.1%	4.7%	4.8%	4.7%	4.7%	4.8%	4.9%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%
FIC	0.0%	0.0%	0.0%	0.9%	0.6%	0.5%	0.5%	0.5%	0.5%	0.7%	0.7%	0.7%
Subtotal, ICDs	100.0%	100.0%	98.4%	98.8%	97.5%	97.4%	98.3%	97.7%	98.2%	97.9%	97.9%	97.8%
NLM	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%
OD	0.0%	0.0%	1.6%	1.1%	1.7%	1.1%	1.2%	1.4%	1.4%	1.9%	1.9%	2.0%
B&F	0.0%	0.0%	0.0%	0.1%	0.8%	1.4%	0.5%	0.7%	0.3%	0.0%	0.0%	0.0%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

NATIONAL INSTITUTES OF HEALTH

National Support for Performance of Medical and Health-Related R&D, by Source of Funds
Fiscal Years 1983-1993
(Dollars in Millions)

Source of Funds	FY 1983	FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991 Estimate	FY 1992 Estimate	FY 1993 Projection
Total	$10,778	$12,155	$13,560	$14,894	$16,931	$18,996	$20,914	$23,094	$25,754	$28,718	$30,827
Government	6,117	6,883	7,669	7,924	9,028	9,725	10,628	11,418	12,429	13,626	14,017
Federal	5,399	6,087	6,791	6,895	7,847	8,431	9,163	9,791	10,602	11,727	11,978
NIH	-4,091	(4,257)	(4,828)	(5,005)	(5,852)	(6,292)	(6,778)	(7,136)	(7,696)	(8,407)	(9,769)
State & local	718	796	878	1,028	1,182	1,294	1,465	1,628	1,828	1,900	2,040
Industry	4,205	4,765	5,352	6,188	7,104	8,433	9,405	10,717	12,234	13,870	15,562
Private nonprofit	456	507	539	782	799	838	881	959	1,091	1,222	1,248
Foundations	89	111	122	129	161	155	129	155	178	236	211
Voluntary health agencies	206	205	233	260	285	323	354	363	393	420	447
Howard Hughes Medical Inst.	54	79	51	247	183	179	197	215	250	273	268
Other	107	112	133	146	170	181	201	226	270	293	322

NOTES:

- This table is unchanged from last years as FY 1994 data is not available for organizations outside NIH. An update will be provided as soon as the data is availab
- Excludes research training and construction.

- These figures report support for the direct conduct of biomedical research. In addition, HHMI's Office of Grants and Special Programs provides support for scientific career development, which is not included here.

Source: NIH Data Book, 1993

NATIONAL INSTITUTES OF HEALTH

Research Centers

Total Awards

(Dollars in Thousands)

INCLUDES AIDS

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Actual	FY 1995 Current Est.	FY 1996 Estimate
NCI	58	59	60	60	56	56	57	88	79	64	69	69
NHLBI	60	60	60	65	64	65	65	65	68	69	73	73
NIDR	13	16	13	16	19	21	22	28	28	29	27	27
NIDDK	45	31	37	38	40	42	42	47	61	59	61	61
NINDS	40	38	38	29	29	30	35	42	44	43	46	43
NIAID	18	17	16	22	26	28	27	27	17	16	15	15
NIGMS	15	13	14	16	10	10	9	8	9	8	9	9
NICHD	43	44	44	44	46	55	64	73	75	77	78	78
NEI	28	29	30	29	29	30	30	29	29	30	30	30
NIEHS	15	15	15	16	16	17	17	18	18	20	20	20
NIA	12	12	14	13	18	31	40	42	50	61	63	63
NIAMS	0	14	23	25	26	26	26	28	28	30	30	30
NIDCD	0	0	0	9	9	12	18	17	15	14	16	16
NIMH	22	25	28	33	37	45	44	53	56	59	59	59
NIDA	4	8	13	16	18	20	22	24	23	33	38	38
NIAAA	9	9	11	10	12	14	14	14	14	14	14	14
NINR	0	0	0	0	4	4	7	7	7	8	7	7
NCRR	185	183	183	190	192	176	198	202	192	198	198	198
NCHGR	0	0	0	0	0	4	9	13	13	12	14	14
FIC	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL, NUMBERS	567	573	599	633	651	686	746	825	826	844	867	864
TOTAL, COSTS	$496,131	$493,660	$561,954	$615,668	$657,767	$702,215	$796,007	$891,772	$903,204	$974,095	$1,015,203	$1,033,720
Average Cost per Center ($ in 1,000s)	$875.0	$861.5	$938.2	$972.6	$1,010.4	$1,023.6	$1,067.0	$1,080.9	$1,093.5	$1,154.1	$1,170.9	$1,196.4
Percent Change in Average Cost		-1.5%	8.9%	3.7%	3.9%	1.3%	4.2%	1.3%	1.2%	5.5%	1.5%	2.2%

NATIONAL INSTITUTES OF HEALTH

RESEARCH TRAINING

INCLUDES AIDS

Number of Full-Time Training Positions

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1990	FY 1991	FY 1992	FY 1993	FY 1993	FY 1994 Actual	FY 1995 Approp.	FY 1996 Estimate
NCI	1,464	1,394	1,475	1,456	1,428	1,485	1,497	1,491	1,446	1,463	1,388	1,388
NHLBI	1,709	1,633	1,666	1,655	1,628	1,519	1,567	1,640	1,557	1,711	1,590	1,558
NIDR	197	192	225	224	189	195	211	205	200	210	210	210
NIDDK	1,046	764	915	916	825	804	843	849	865	905	945	843
NINDS	623	579	653	544	546	564	503	516	504	536	522	522
NIAID	518	487	491	561	579	711	754	732	801	818	818	829
NIGMS	3,396	3,238	3,566	3,587	3,702	3,838	4,215	4,333	4,325	4,441	4,567	4,567
NICHD	702	728	736	723	640	677	723	743	767	727	750	750
NEI	220	232	229	252	251	258	261	262	280	261	270	270
NIEHS	483	446	462	460	434	481	556	467	460	482	482	482
NIA	227	263	313	344	387	426	418	436	458	470	472	472
NIAMS	0	223	242	238	219	228	215	233	218	238	239	239
NIDCD	0	0	0	96	105	112	142	166	189	203	203	203
NIMH	914	882	993	1,000	1,077	1,163	1,218	1,242	1,289	1,251	1,251	1,251
NIDA	79	79	114	114	114	174	276	297	302	345	354	354
NIAAA	69	71	123	129	120	147	160	141	149	195	189	199
NINR	0	153	167	186	219	257	269	281	233	208	205	205
NCRR	39	36	41	67	73	82	82	82	80	76	76	76
NCHGR	0	0	0	0	0	130	158	171	170	166	123	123
FIC	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	11,686	11,400	12,411	12,572	12,536	13,271	14,066	14,267	14,291	14,706	14,654	14,541
Average Cost per FTTP ($ in 1,000s)	$20.4	$20.4	$20.7	$20.9	$22.6	$24.0	$24.3	$24.4	$24.5	$25.3	$26.0	$26.9
Percent Change in Av. Cost		0.1%	1.1%	1.2%	7.9%	6.4%	1.2%	0.3%	0.6%	3.2%	2.7%	3.3%

SUCCESS RATES TABLE 1

NATIONAL INSTITUTES OF HEALTH

Success Rates - Research Project Grants

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Actual	FY 1995 Cur. Est.	FY 1996 Estimate
NCI	32.0%	30.2%	34.2%	32.7%	25.0%	23.5%	27.5%	32.2%	24.6%	21%	22%	19%	21%
NHLBI	32.4%	31.4%	32.6%	31.4%	25.7%	24.9%	27.5%	29.2%	21.9%	23%	23%	24%	19%
NIDR	34.4%	33.5%	28.5%	25.4%	23.9%	21.0%	30.0%	27.1%	24.3%	28%	37%	29%	31%
NIDDK	31.9%	33.1%	38.0%	31.8%	26.3%	23.0%	26.8%	32.7%	22.0%	25%	25%	25%	18%
NINDS	33.9%	34.0%	39.4%	39.6%	31.7%	24.2%	29.9%	26.6%	25.1%	26%	26%	27%	24%
NIAID	33.6%	32.0%	34.1%	30.6%	30.1%	27.4%	31.0%	30.0%	29.4%	24%	25%	25%	28%
NIGMS	42.9%	40.1%	38.0%	38.5%	28.3%	22.0%	34.4%	35.7%	29.8%	32%	33%	40%	35%
NICHD	24.9%	23.9%	33.2%	24.6%	24.6%	19.3%	25.1%	26.3%	21.3%	19%	21%	17%	17%
NEI	46.6%	46.5%	49.5%	42.9%	42.8%	37.5%	32.8%	31.0%	32.1%	36%	40%	33%	30%
NIEHS	27.8%	25.7%	28.9%	28.5%	26.5%	28.3%	27.5%	28.0%	21.1%	25%	26%	17%	22%
NIA	27.8%	25.0%	27.7%	25.4%	23.6%	21.6%	30.4%	28.9%	23.1%	23%	25%	24%	28%
NIAMS	n/a	30.6%	28.5%	26.1%	26.4%	20.0%	31.3%	17.5%	20.9%	17%	20%	20%	21%
NIDCD	n/a	n/a	n/a	39.7%	38.2%	36.9%	30.9%	30.2%	29.3%	30%	32%	27%	25%
NIMH	30.4%	26.0%	33.2%	28.7%	29.2%	24.4%	27.3%	26.9%	19.5%	22%	21%	19%	18%
NIDA	41.1%	37.8%	48.1%	17.3%	36.7%	36.7%	31.2%	30.9%	31.8%	33%	33%	26%	21%
NIAAA	30.3%	30.2%	35.5%	26.9%	38.0%	34.3%	22.9%	31.3%	19.2%	27%	29%	21%	18%
NINR	n/a	22.1%	30.0%	26.9%	18.9%	16.4%	19.2%	15.4%	11.3%	10%	12%	11%	12%
NCRR	n/a	n/a	n/a	n/a	n/a	21.6%	28.8%	32.7%	28.4%	16%	18%	23%	26%
NCHGR	n/a	n/a	n/a	n/a	31.8%	23.3%	37.9%	21.6%	27.9%	24%	28%	19%	25%
FIC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	100%	27%	38%	24%
NIH	33.4%	32.1%	34.9%	32.4%	27.6%	24.0%	29.3%	29.6%	24.5%	24%	25%	24%	23%

The FY 1996 President's Budget Request reflects the FY 1994 realignment of the NIH mechanism structure to include R03s and R21s in RPGs and to display SBIR/STTRs separately within RPGs to exclude these setaside programs from RPG analytical calculations including success rates and average costs. "FY 1994 Comp." is comparable to historical data.

NATIONAL INSTITUTES OF HEALTH
Competing Research Projects
Success Rates

SUCCESS RATES TABLE 2

Includes AIDS

	FY 1994 Actual			FY 1995 Current Estimate			FY 1996 Estimate		
Institute	New	Renewals	Total	New	Renewals	Total	New	Renewals	Total
NCI	16%	36%	22%	13%	41%	19%	17%	35%	21%
NHLBI	19%	36%	23%	20%	37%	24%	16%	29%	19%
NIDR	35%	43%	37%	28%	32%	29%	30%	34%	31%
NIDDK	20%	41%	25%	21%	32%	25%	14%	33%	18%
NINDS	20%	42%	26%	24%	32%	27%	19%	37%	24%
NIAID	20%	40%	25%	21%	41%	25%	22%	45%	28%
NIGMS	23%	51%	33%	27%	56%	40%	26%	53%	35%
NICHD	17%	33%	21%	14%	29%	17%	14%	33%	17%
NEI	31%	50%	40%	23%	46%	33%	22%	43%	30%
NIEHS	22%	35%	26%	15%	23%	17%	18%	36%	22%
NIA	21%	40%	25%	20%	36%	24%	26%	36%	28%
NIAMS	16%	36%	20%	16%	33%	20%	17%	37%	21%
NIDCD	26%	47%	32%	22%	37%	27%	21%	35%	25%
NIMH	17%	39%	21%	16%	35%	19%	15%	42%	18%
NIDA	29%	46%	33%	18%	49%	26%	15%	42%	21%
NIAAA	24%	46%	29%	14%	54%	21%	14%	40%	18%
NINR	12%	21%	12%	10%	25%	11%	12%	30%	12%
NCRR	15%	47%	18%	17%	100%	23%	21%	70%	26%
NCHGR	23%	45%	28%	16%	24%	19%	22%	37%	25%
FIC	26%	67%	27%	36%	50%	38%	24%	24%	24%
Total, NIH	20%	42%	25%	19%	40%	24%	18%	39%	23%

AIDS Only - 9% of competing RPGs; only NIAID and NIDA > 50 grants; only NIAID > 30 renewals.

SUCCESS RATES TABLE 3

	FY 1994 Actual			FY 1995 Current Estimate			FY 1996 Estimate		
Institute	New	Renewals	Total	New	Renewals	Total	New		Total
NCI	19%	8%	17%	14%	62%	19%	13%	40%	22%
NHLBI	64%	56%	63%	49%	40%	48%	23%	75%	29%
NIDR	73%	0%	73%	0%	50%	50%	50%	0%	50%
NIDDK	26%	0%	26%	14%	0%	14%	18%	0%	18%
NINDS	32%	25%	30%	26%	25%	26%	39%	25%	36%
NIAID	29%	64%	36%	28%	63%	35%	28%	59%	34%
NIGMS	23%	57%	33%	0%	40%	40%	20%	47%	31%
NICHD	25%	50%	28%	17%	67%	24%	11%	73%	21%
NEI	38%	50%	42%	33%	33%	33%	33%	29%	30%
NIEHS	0%	0%	0%	0%	100%	100%	100%	0%	100%
NIA	100%	0%	100%	75%	0%	75%	100%	0%	100%
NIAMS	0%	0%	0%	20%	17%	17%	20%	0%	20%
NIDCD	25%	0%	25%	50%	0%	50%	50%	0%	50%
NIMH	30%	41%	33%	17%	23%	19%	27%	41%	31%
NIDA	39%	60%	44%	29%	64%	40%	26%	93%	40%
NIAAA	23%	40%	28%	18%	18%	18%	18%	18%	18%
NINR	18%	0%	18%	3%	0%	3%	23%	0%	23%
NCRR	50%	100%	67%	100%	100%	100%	100%	100%	100%
NCHGR	0%	0%	0%	0%	0%	0%	0%	0%	0%
FIC	57%	0%	57%	44%	100%	45%	20%	0%	20%
Total, NIH	31%	51%	34%	25%	54%	30%	25%	55%	31%

Excludes AIDS

SUCCESS RATES TABLE 4

	FY 1994 Actual			FY 1995 Current Estimate			FY 1996 Estimate		
Institutes	New	Renewals	Total	New	Renewals	Total	New	Renewals	Total
NCI	18%	40%	23%	13%	41%	19%	17%	35%	21%
NHLBI	18%	36%	22%	19%	37%	23%	16%	29%	19%
NIDR	32%	43%	35%	28%	31%	29%	29%	34%	30%
NIDDK	20%	41%	25%	22%	32%	25%	14%	33%	18%
NINDS	20%	43%	26%	24%	32%	27%	19%	37%	24%
NIAID	17%	33%	21%	17%	35%	22%	20%	41%	25%
NIGMS	23%	51%	33%	27%	56%	40%	26%	53%	36%
NICHD	17%	32%	20%	14%	27%	17%	14%	31%	17%
NEI	31%	50%	40%	23%	46%	33%	22%	44%	30%
NIEHS	22%	35%	26%	15%	22%	17%	18%	36%	22%
NIA	21%	40%	25%	20%	36%	24%	25%	36%	28%
NIAMS	16%	36%	20%	16%	35%	20%	17%	37%	21%
NIDCD	26%	47%	32%	22%	37%	27%	20%	35%	25%
NIMH	17%	39%	20%	16%	36%	19%	14%	42%	18%
NIDA	25%	42%	30%	15%	43%	22%	13%	36%	19%
NIAAA	24%	49%	29%	14%	58%	21%	14%	42%	18%
NINR	11%	21%	12%	11%	25%	12%	10%	30%	11%
NCRR	15%	43%	17%	16%	100%	22%	20%	67%	24%
NCHGR	23%	45%	28%	18%	24%	19%	22%	37%	25%
FIC	24%	67%	25%	34%	48%	36%	26%	24%	26%
Total, NIH	20%	41%	25%	18%	40%	24%	18%	38%	22%

NATIONAL INSTITUTES OF HEALTH
Single-Investigator Research Project Grants
Success Rates

SUCCESS RATES TABLE 5

Includes AIDS

	FY 1994 Actual			FY 1995 Current Estimate			FY 1996 Estimate		
Institute	New	Renewals	Total	New	Renewals	Total	New	Renewals	Total
NCI	17%	35%	21%	14%	35%	18%	16%	28%	19%
NHLBI	19%	34%	22%	18%	35%	22%	14%	29%	18%
NIDR	30%	43% *	34%	21% *	35% *	25%	23%	37% *	27%
NIDDK	18%	40%	24%	22%	34%	26%	15%	30%	19%
NINDS	20%	43%	26%	24%	32%	27%	19%	38%	24%
NIAID	20%	39%	24%	20%	41%	25%	22%	44%	27%
NIGMS	22%	51%	33%	26%	55%	38%	25%	53%	35%
NICHD	15%	32%	19%	12%	34%	17%	12%	34%	17%
NEI	31%	50%	39%	20%	58%	33%	19%	53%	30%
NIEHS	19%	35% *	23%	14%	26% *	16%	19%	33% *	22%
NIA	19%	37%	22%	19%	33%	22%	23%	35%	26%
NIAMS	15%	36%	19%	15%	36%	19%	14%	38%	19%
NIDCD	24%	47%	31%	20%	36%	25%	18%	35%	24%
NIMH	17%	38%	21%	16%	35%	19%	15%	38%	19%
NIDA	28%	46%	33%	27%	26%	27%	23%	21%	22%
NIAAA	22%	46%	28%	17%	31% *	20%	12%	30% *	16%
NINR	11% *	22% *	11% *	11% *	28% *	12% *	11% *	35% *	12% *
NCRR	30% *	47% *	35% *	31% *	32% *	31% *	27% *	35% *	31% *
NCHGR	24% *	44% *	29% *	17% *	24% *	18% *	20% *	31% *	22% *
FIC	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *
Total, NIH	19%	41%	25%	18%	39%	24%	17%	37%	22%

SUCCESS RATES TABLE 6

AIDS Only

	FY 1994 Actual			FY 1995 Current Estimate			FY 1996 Estimate		
Institute	New	Renewals	Total	New	Renewals	Total	New	Renewals	Total
NCI	17% *	35% *	21% *	20% *	42% *	24% *	24% *	39% *	26% *
NHLBI	27% *	22% *	26% *	18% *	25% *	18% *	0% *	0% *	0% *
NIDR	71% *	0% *	71% *	0% *	50% *	50% *	100% *	100% *	0% *
NIDDK	26% *	0% *	26% *	10% *	100% *	14% *	15% *	100% *	18% *
NINDS	31% *	29% *	30% *	23% *	50% *	26% *	36% *	25% *	33% *
NIAID	28%	63%	35%	27%	62%	34%	27%	58%	33%
NIGMS	23% *	62% *	33% *	0% *	40% *	40% *	25% *	40% *	31% *
NICHD	6% *	0% *	5% *	20% *	43% *	22% *	14% *	25% *	17% *
NEI	29% *	50% *	36% *	33% *	33% *	33% *	33% *	29% *	30% *
NIEHS	0% *	0% *	0% *	0% *	100% *	100% *	100% *	0% *	100% *
NIA	0% *	100% *	100% *	0% *	100% *	100% *	0% *	100% *	100% *
NIAMS	0% *	0% *	0% *	17% *	0% *	17% *	0% *	0% *	0% *
NIDCD	0% *	0% *	0% *	100% *	0% *	100% *	50% *	0% *	50% *
NIMH	28% *	48% *	32% *	17% *	29% *	20% *	27% *	43% *	31% *
NIDA	38%	71% *	44%	41% *	40% *	41%	39% *	43% *	40%
NIAAA	23% *	40% *	28% *	18% *	18% *	18% *	18% *	18% *	18% *
NINR	15% *	0% *	15% *	3% *	0% *	3% *	23% *	0% *	23% *
NCRR	50% *	0% *	50% *	100% *	0% *	100% *	100% *	0% *	100% *
NCHGR	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *
FIC	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *	0% *
Total, NIH	27%	55%	32%	24%	50%	29%	26%	47%	30%

Note: Single Investigator = R01s, R37s, and R29s.
*= <50 awards.

DHHS – NATIONAL INSTITUTES OF HEALTH

STATISTICAL DATA – RESEARCH GRANTS, DIRECT AND INDIRECT COSTS AWARDED 1/
(Dollars in Thousands)

Fiscal Year	Direct Costs Awarded	Indirect Costs Awarded	Total Dollars Awarded	Percent To Total In Dollars		Percent Growth In Dollars	
				Direct	Indirect	Direct	Indirect
1981	$1,568,995	$655,143	$2,224,138	70.5	29.5	--	--
1982	1,610,679	689,855	2,300,534	70.0	30.0	2.7	5.3
1983	1,793,207	791,580	2,584,787	69.4	30.6	11.3	14.7
1984	2,036,639	921,627	2,958,266	68.8	31.2	13.6	16.4
1985	2,343,216	1,069,707	3,412,923	68.7	31.3	15.1	16.1
1986	2,444,946	1,119,115	3,564,061	68.6	31.4	4.3	4.6
1987	2,876,830	1,311,539	4,188,369	68.7	31.3	17.7	17.2
1988	3,124,042	1,416,716	4,540,758	68.8	31.2	8.6	8.0
1989	3,315,563	1,530,547	4,846,110	68.4	31.6	6.1	8.0
1990	3,428,392	1,599,286	5,027,678	68.2	31.8	3.4	4.5
1991	3,748,778	1,744,378	5,493,156	68.2	31.8	9.3	9.1
1992	4,169,928	1,896,215	6,066,143	68.7	31.3	11.2	8.7
1993	4,888,871	2,183,265	7,072,136	69.1	30.9	17.2	15.1
1994	5,098,605	2,279,984	7,378,589	69.1	30.9	4.3	4.4
1995 Estimate	5,302,435	2,371,132	7,673,567	69.1	30.9	4.0	4.0
1996 Estimate	5,505,938	2,462,135	7,968,073	69.1	30.9	3.8	3.8

Note – – 1992 and prior years data excludes NIMH, NIAAA, and NIDA. Comparable data is not available.

1/ Actual data from the Indirect Cost Management System (ICMS). Includes research project grants, research centers, research career awards, organ systems, clinical education, cooperative clinical research, minority biomedical research support and cancer control grants.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Full-Time Equivalents

ICD	FY 1994 Actual			FY 1995 Estimate			FY 1996 President's Budget		
	AIDS	Non-AIDS	Total	AIDS	Non-AIDS	Total	AIDS	Non-AIDS	Total
NCI	301	2,081	2,382	292	2,023	2,315	281	2,008	2,289
NHLBI	15	839	852	15	842	857	15	832	847
NIDR	22	320	342	22	329	351	22	327	349
NIDDK	10	587	597	10	611	621	10	610	620
NINDS	34	635	669	34	646	680	34	639	673
NIAID	383	719	1,102	383	724	1,107	379	717	1,096
NIGMS	2	177	179	2	180	182	2	177	179
NICHD	24	480	504	24	484	508	24	479	503
NEI	8	245	253	8	242	250	8	239	247
NIEHS	8	694	702	8	699	707	8	693	701
NIA	4	444	448	4	440	444	4	435	439
NIAMS	3	147	150	3	144	147	3	142	145
NIDCD	0	125	125	1	113	114	1	112	113
NIMH	44	856	900	38	859	897	38	850	888
NIDA	78	308	386	70	316	386	70	312	382
NIAAA	6	228	234	6	229	235	6	227	233
NINR	7	46	53	7	43	50	7	43	50
NCRR	11	87	98	11	89	100	11	87	98
NCHGR	0	139	139	0	196	196	0	196	196
FIC	4	64	68	4	72	76	4	71	75
Subtotal	964	9,221	10,183	942	9,281	10,223	927	9,196	10,123
NLM	10	586	596	10	576	586	10	570	580
OD	41	659	700	65	640	705	66	620	686
Subtotal	1,015	10,466	11,479	1,017	10,497	11,514	1,003	10,386	11,389
Central Services	326	4,430	4,756	328	4,341	4,669	326	4,356	4,682
Subtotal, NIH	1,341	14,896	16,235	1,345	14,838	16,183	1,329	14,742	16,071
Undistributed FTEs	0	0	0	0	0	14	0	0	64
Total, NIH	1,341	14,896	16,235	1,345	14,838	16,197	1,329	14,742	16,135

NHLBI's FY 1994 Actuals were adjusted downward by 2 in order to make the numbers comparable to FY 1995 and 1996to accou
a transfer to HRSA for the Bone Marrow Program.

NATIONAL INSTITUTES OF HEALTH

Research Project Grants

Total Number of Awards and Dollars

(Dollars in Thousands)

INCLUDES AIDS

	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Bud. Auth.	FY 1995 Current Est.	FY 1996 Estimate
No. of Awards:													
Competing	6,825	6,739	7,197	6,867	6,157	5,620	6,462	6,768	6,149	6,822	6,474	6,568	6,046
Sub-total (includes Noncom	19,710	20,220	21,300	22,017	22,725	22,527	23,352	24,033	23,952	24,401	24,076	23,852	23,874
SBIR											914	1,042	1,195
Total	19,710	20,220	21,300	22,017	22,725	22,527	23,352	24,033	23,952	24,401	24,990	24,894	25,069
Average Annual Cost:													
Competing	$145.2	$148.3	$171.9	$175.2	$182.3	$196.7	$208.1	$216.7	$218.3	$223.3	$225.0	$232.5	$249.3
Total (includes Noncomp)	$149.7	$154.4	$175.1	$183.0	$193.9	$205.3	$216.1	$227.2	$236.2	$244.1	$244.0	$251.6	$260.9
Percent Change from prior year:													
Competing		2.2%	15.9%	1.9%	4.0%	7.9%	5.8%	4.2%	0.7%	2.3%	3.1%	3.3%	7.2%
Total		3.1%	13.4%	4.5%	5.9%	5.9%	5.2%	5.1%	4.0%	3.4%	3.3%	3.1%	3.7%
Average Length of Award in Years	3.3	3.6	3.8	4.0	4.1	4.1	3.9	3.9	3.9	3.9	3.9	3.9	3.9

The FY 1996 President's Budget Request reflects the FY 1994 realignment of the NIH mechanism structure to include R03s and R21s in RPGs and to display SBIR/STTRs separately within RPGs to exclude these setaside programs from RPG analytical calculations including success rates and average costs. "FY 1994 Comp." is comparable to historical data.

DHHS -- NATIONAL INSTITUTES OF HEALTH
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1938 - 1995
(Dollars in Thousands)
(Current Appropriations Only)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
1938	$400	......	......	......	......	......	......	......	......	......	......	......
1939	400	......	......	......	......	......	......	......	......	......	......	......
1940	570	......	......	......	......	......	......	......	......	......	......	......
1941	570	......	......	......	......	......	......	......	......	......	......	......
1942	565	......	......	......	......	......	......	......	......	......	......	......
1943	535	......	......	......	......	......	......	......	......	......	......	......
1944	530	......	......	......	......	......	......	......	......	......	......	......
1945	561	......	......	......	......	......	......	......	......	......	......	......
1946	549	......	......	......	......	......	......	......	......	......	......	......
1947	1,821	......	......	......	......	......	......	......	......	......	......	......
1948	14,500	......	......	......	......	......	......	......	......	......	......	......
1949	14,000	......	......	......	......	......	......	......	......	......	......	......
1950	18,900	$10,725	$1,780	......	......	......	......	......	......	......	......	......
1951	20,086	14,200	1,955	......	......	......	......	......	......	......	......	......
1952	19,657	10,083	1,618	......	......	......	......	......	......	......	......	......
1953	17,887	12,000	1,650	......	......	......	......	......	......	......	......	......
1954	20,237	15,168	1,740	$7,000	$4,500	$5,738	......	......	......	......	......	......
1955	21,737	16,668	1,990	8,270	7,601	6,180	......	......	......	......	......	......
1956	24,978	18,898	2,176	10,840	9,861	7,775	......	......	......	......	......	......
1957	48,432	33,396	6,026	15,885	18,650	13,299	......	......	......	......	......	......
1958	56,402	35,936	6,430	20,385	21,387	17,400	......	......	......	......	......	......
1959	75,268	45,613	7,420	31,215	29,403	24,071	......	......	......	......	......	......
1960	91,257	62,237	10,019	46,862	41,487	34,054	......	......	......	......	......	......
1961	111,000	86,900	15,500	61,200	56,600	44,000	......	......	......	......	......	......
1962	142,836	132,912	17,340	81,831	70,812	56,091	......	......	......	......	......	......
1963	155,742	147,398	21,199	103,388	83,506	66,142	......	......	......	......	......	......
1964	144,340	132,404	19,689	113,679	87,675	68,723	......	-34,000 1/	......	......	......	......
1965	150,011	124,824	20,083	113,050	87,821	69,847	......	42,696	......	......	......	......
1966	163,768	141,462	23,677	123,203	101,153	77,987	$127,168	55,024	......	......	......	......
1967	175,656	164,770	28,308	135,687	116,296	90,670	145,113	64,922	......	$24,298	......	......
1968	183,356	167,954	30,307	143,954	128,633	94,422	160,284	68,621	......	17,289	......	......
1969	185,150	166,928	29,984	143,888	128,935	96,841	163,514	73,127	......	17,820	......	......
1970	181,454	160,634	28,754	131,761	97,315 3/	97,342	148,294	76,095	$22,828	17,423	......	......
1971	233,160	194,925	35,440	137,986	103,502	102,368	160,194	94,760	30,032	20,151	......	......
1972	378,794	232,627	43,388	153,337	116,732	109,117	173,474	116,427	37,132	26,436	......	......
1973	492,205	300,000	46,991	167,316	130,672	113,414	183,171	130,429	38,562	30,956	......	......
1974	527,486	289,550	43,959	153,561	121,358	111,089	168,329	125,455	41,177	28,397	......	......
1975	691,666	324,630	50,033	173,514	142,498	119,452	187,400	142,435	44,133	35,171	......	......

FISCAL YEAR	NIDCD	NIMH	NIDA	NIAAA	NCRR	NINR	NCHGR	FIC	NLM	OD	B&F	TOTAL
1938	......	......	......	......	$64	......	......	......	......	......	......	$464
1939	......	......	......	......	64	......	......	......	......	......	......	464
1940	......	......	......	......	137	......	......	......	......	......	......	707
1941	......	......	......	......	141	......	......	......	......	......	......	711
1942	......	......	......	......	135	......	......	......	......	......	......	700
1943	......	......	......	......	743	......	......	......	......	......	......	1,278
1944	......	......	......	......	2,025	......	......	......	......	......	......	2,555
1945	......	......	......	......	2,274	......	......	......	......	......	......	2,835
1946	......	......	......	......	2,866	......	......	......	......	......	......	3,415
1947	......	......	......	......	6,254	......	......	......	......	......	......	8,075
1948	......	......	......	......	10,126	......	......	......	......	......	......	24,626
1949	......	......	......	......	14,540	......	......	......	......	......	......	28,540
1950	......	......	......	......	12,075	......	......	......	......	......	......	43,480
1951	......	......	......	......	14,314	......	......	......	......	......	......	50,555
1952	......	......	......	......	15,757	......	......	......	......	......	......	47,115
1953	......	......	......	......	16,599	......	......	......	......	......	......	48,136
1954	......	......	......	......	4,675	......	......	......	......	......	......	59,058
1955	......	......	......	......	4,675	......	......	......	......	......	......	67,121
1956	......	......	......	......	5,929	......	......	......	......	......	......	80,457
1957	......	......	......	......	12,122	......	......	......	......	......	......	147,810
1958	......	......	......	......	14,026	......	......	......	......	......	......	171,966
1959	......	......	......	......	28,974	......	......	......	......	......	......	241,964
1960	......	......	......	......	45,994	......	......	......	......	......	......	331,910
1961	......	......	......	......	83,900	......	......	......	......	......	......	459,100
1962	......	......	......	......	127,637	......	......	......	......	......	......	629,459
1963	......	......	......	......	159,626	......	......	......	......	......	......	737,201
1964	......	......	......	......	163,869	......	......	......	......	......	......	730,379
1965	......	......	......	......	164,759	......	......	......	......	......	......	773,091
1966	......	......	......	......	60,469 2/	......	......	......	......	......	......	873,931
1967	......	......	......	......	68,534	......	......	......	......	......	......	1,014,254
1968	......	......	......	......	81,141	......	......	$500	......	......	......	1,076,461
1969	......	......	......	......	84,810	......	......	600	$18,160	......	......	1,109,757
1970	......	......	......	......	67,925 4/	......	......	2,775	19,251	$7,541 5/	$1,615 6/	1,061,007
1971	......	......	......	......	66,320	......	......	3,666	21,440	8,903	......	1,212,847
1972	......	......	......	......	74,981	......	......	4,307	24,127	11,712	3,565	1,506,156
1973	......	......	......	......	75,073	......	......	4,666	26,566	12,042	6,500	1,762,565
1974	......	......	......	......	129,426	......	......	4,767	25,871	12,000	8,000	1,790,425
1975	......	......	......	......	127,200	......	......	5,589	28,850	17,326	3,000	2,092,897

DHHS – NATIONAL INSTITUTES OF HEALTH
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1938 - 1995
(Dollars In Thousands)
(Current Appropriations Only)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
1976..................	761,727	370,013	51,291	179,516	144,446	126,852	187,312	136,404	50,212	37,660	$19,288	......
1976 T.Q..........	152,901	58,763	7,854	43,719	34,272	27,638	34,078	24,201	4,036	9,519	8,743	......
1977..................	815,000	396,661	55,573	219,600	155,500	141,000	205,000	145,543	64,000	51,141	30,000	......
1978..................	872,388	447,909	61,728	260,253	178,438	162,341	230,796	166,390	85,400	64,241	37,305	......
1979..................	937,129	510,526	65,213	302,767	212,365	191,328	277,628	197,630	105,192	78,080	56,911	......
1980..................	999,869	527,488	68,303	341,206	241,966	215,364	312,468	206,953	112,989	83,893	69,966	......
1981..................	989,355	549,693	71,114	369,462	252,533	232,077	333,764	220,628	117,983	93,491	75,608	......
1982..................	986,617	559,637	71,983	368,191	265,901	235,895	339,862	226,309	127,374	106,270	81,903	......
1983..................	987,642	624,259	79,292	413,492	297,064	279,129	369,613	254,324	141,901	164,867	93,996	......
1984..................	1,081,581	704,939	88,674	464,026	335,863	319,596	415,937	276,046	155,131	180,597	115,292	......
1985..................	1,183,806	805,269	100,688	543,576	396,885	370,965	482,260	313,295	181,678	194,819	144,521	......
1986..................	1,203,369	822,292	98,841	544,858	414,727	366,964	492,630	307,958	186,705	186,986	149,762	......
1987..................	1,402,837	930,001	117,945	511,124	490,233	545,523	570,916	366,760	216,637	209,294	177,661	$138,713
1988..................	1,469,327	965,536	126,297	534,733	534,692	638,800	632,676	396,611	224,947	215,666	194,746	147,679
1989..................	1,570,349	1,045,509	130,709	559,494	472,291	740,257	682,213	425,375	231,170	223,403	222,639	159,891
1990..................	1,634,332	1,072,354	135,749	581,477	490,409	832,977	661,782	442,914	236,533	229,234	239,455	168,930
1991..................	1,714,784	1,126,942	148,918	615,272	541,743	906,251	760,010	478,956	253,241	241,028	323,752	193,247
1992..................	1,962,587	1,188,593	158,417	658,925	577,938	959,062	816,844	518,251	268,978	246,575	383,382	203,047
1993..................	1,981,351	1,214,793	161,301	681,342	600,078	979,471	832,581	527,788	276,168	251,187	399,924	212,456
1994..................	2,082,267	1,277,880	169,520	716,054	630,650	1,065,583	875,511	555,195	290,260	264,249	420,303	223,260
1995..................	2,135,119	1,313,957	174,392	738,380	650,467	1,094,258	904,925	571,519	299,973	272,733	434,038	231,258

NOTE: Includes $10,000, transferred from "Special Cancer Research" appropriation.

1/ Congress authorized the transfer of $34,000 from other NIH appropriations to establish the "National Institute of Child Health and Human Development.

2/ Excludes the "National Institute of General Medical Sciences" established as a separate appropriation. ,

3/ Excludes funds for blindness, established as a separate appropriation "National Eye Institute".

4/ Excludes the "Office of International Operations", transferred to the "National Institute of Allergy and Infectious Diseases" and "John E. Fogarty International Center for Advanced Study in the Health Sciences".

5/ Prior to 1970, previously funded under NIH Management Fund.

6/ Prior to 1970, previously funded under DHEW health activities.

7/ Reflects a 1.2% administrative reduction and procurement reform and transfer to OASH for AZT.

8/ Reflects reductions for Extramural Salary Cap, Procurement Reform, S&E, and Sequestration.

9/ Reflects 2.41% reduction and NIH's share of the $50M reduction for Salaries and Expenses.

10/ Reflects reductions for travel and Salaries and Expenses.

11/ Reflects an across the board .8 percent reduction and reductions for Salaries and Expenses and Consultant Services. Reflects real transfer of $1,000 from NCI to FDA.

12/ National Center of Nursing Research elevated to Institute status in 1994.
NCRR excludes $1.0M in Emergency Supplemental for Earthquake Relief.

13/ Excludes enacted reductions of $7,446 for procurement, $345 for rent, and $4,401 Bonus pay.
NRCC includes proposed rescission of $1,000 in construction funds.

FISCAL YEAR	NIDCD	NIMH	NIDA	NIAAA	NCRR	NINR	NCHGR	FIC	NLM	OD	B&F	TOTAL
1976.................	......	......	......	......	130,265	....	....	5,705	29,065	18,370	54,000	2,302,126
1976 T.Q..........	......	......	......	......	20,282	....	....	1,135	6,572	4,642	750	439,107
1977.................	......	......	......	......	137,500	....	....	7,992	35,234	16,934	67,400	2,544,078
1978.................	......	......	......	......	145,095	....	....	8,483	37,619	18,900	65,650	2,842,938
1979.................	......	......	......	......	154,164	....	....	8,989	41,431	19,673	30,950	3,189,976
1980.................	......	......	......	......	169,196	....	....	8,987	43,979	21,036	3,250	3,428,935
1981.................	......	......	......	......	175,627	....	....	9,124	44,666	22,531	11,750	3,569,406
1982.................	......	......	......	......	184,177	....	....	9,205	45,035	23,618	9,898	3,641,875
1983.................	......	......	......	......	213,917	....	....	10,147	51,943	24,683	17,500	4,023,969
1984.................	......	......	......	......	243,177	....	....	11,336	49,613	26,720	25,040	4,493,588
1985.................	......	......	......	......	304,025	....	....	11,728	55,910	38,304	21,730	5,149,459
1986.................	......	......	......	......	292,523	....	....	11,054	55,322	111,961	14,259	5,262,211
1987.................	......	......	......	......	322,860	$20,000	....	11,420	61,838	57,208	31,900	6,182,910
1988.................	......	......	......	......	368,153	23,380	....	15,651	67,910	61,819	47,870	6,666,693
1989.................	$94,166	......	......	......	358,076	29,133	....	15,790	73,731	72,076	38,492	7,144,764 7/
1990.................	117,583	......	......	......	353,734	33,513	$59,538	15,516	81,861	107,419	61,042	7,576,352 8/
1991.................	134,935	......	......	......	335,255	39,722	87,418	17,519	91,408	97,651	168,687	8,276,739 9/
1992.................	148,789	......	......	......	314,213	44,929	104,762	19,593	99,088	141,854	103,840	8,921,687 10/
1993.................	154,814	$583,651	$403,806	$176,619	312,468	48,119	106,239	19,733	113,031	190,325	108,731	10,335,996 11/
1994.................	162,823	613,444	425,201	185,617	331,915	51,018	128,701	21,677	119,981	233,605	111,039	10,955,773 12/
1995.................	168,313	632,424	437,643	190,997	359,367	52,757	152,849	23,775	128,694	239,948	114,120	11,321,906 13/

DHHS-NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
NIH TOTAL

Budget Authority by Object

	FY 1995 Current/Estimate	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$450,751,000	$463,270,000	+$12,519,000
Other than full-time permanent	106,383,000	110,179,000	+3,796,000
Other personnel compensation	22,792,000	23,571,000	+779,000
Special personnel services	71,165,000	73,896,000	+2,731,000
Total, Personnel Compensation	651,091,000	670,916,000	+19,825,000
Personnel Benefits:			
Civilian personnel benefits	137,956,000	141,917,000	+3,961,000
Benefits for former personnel	2,260,000	1,584,000	-676,000
Travel and transportation of persons	19,080,000	19,899,000	+819,000
Transportation of things	3,731,000	3,852,000	+121,000
Rental Payments to GSA	5,590,000	5,705,000	+115,000
Rental payments to others	4,576,000	4,735,000	+159,000
Communications, utilities, and miscellaneous charges	43,288,000	44,404,000	+1,116,000
Printing and reproduction	17,053,000	17,734,000	+681,000
Consulting services	18,647,000	21,052,000	+2,405,000
Other services	358,771,000	405,375,000	+46,604,000
Purchases from Govt Accts	738,872,000	775,504,000	+36,632,000
Operation of GOCOs	71,594,000	71,596,000	+2,000
R&D Contracts	817,568,000	850,747,000	+33,179,000
Supplies and materials	128,208,000	131,451,000	+3,243,000
Equipment	72,988,000	75,505,000	+2,517,000
Lands and structures	26,000	26,000	—
Grants, subsidies, and contributions	8,212,382,000	8,529,179,000	+316,797,000
Insurance claims and indemnities	1,704,000	1,724,000	+20,000
Interest and dividends	161,000	161,000	—
Total Obligations	11,305,546,000	11,773,066,000	+467,520,000

DHHS-NATIOANL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
NON-AIDS

Budget Authority by Object

	FY 1995 Current/Estimate	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$410,837,000	$422,075,000	+$11,238,000
Other than full-time permanent	96,537,000	99,966,000	+3,429,000
Other personnel compensation	20,560,000	21,258,000	+698,000
Special personnel services	66,818,000	69,388,000	+2,570,000
Total, Personnel Compensation	594,752,000	612,687,000	+17,935,000
Personnel Benefits:			
Civilian personnel benefits	124,619,000	128,210,000	+3,591,000
Benefits for former personnel	2,144,000	1,550,000	-594,000
Travel and transportation 'of persons	16,263,000	17,005,000	+742,000
Transportation of things	3,303,000	3,432,000	+129,000
Rental Payments to GSA	4,255,000	4,332,000	+77,000
Rental payments to others	4,051,000	4,190,000	+139,000
Communications, utilities, and miscellaneous charges	39,709,000	40,736,000	+1,027,000
Printing and reproduction	16,152,000	16,813,000	+661,000
Consulting services	13,801,000	16,286,000	+2,485,000
Other services	295,573,000	340,174,000	+44,601,000
Purchases from Govt Accts	635,074,000	667,431,000	+32,357,000
Operation of GOCOs	43,067,000	43,119,000	+52,000
R&D Contracts	579,057,000	600,871,000	+21,814,000
Supplies and materials	103,669,000	106,138,000	+2,469,000
Equipment	63,905,000	65,996,000	+2,091,000
Lands and structures	26,000	26,000	---
Grants, subsidies, and 'contributions	7,428,680,000	7,694,510,000	+265,830,000
Insurance claims and 'indemnities	1,704,000	1,724,000	+20,000
Interest and dividends	16,000	12,000	-4,000
Total Obligations	9,969,820,000	10,365,242,000	+395,422,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
AIDS

Budget Authority by Object

	FY 1995 Current/Estimate	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$39,914,000	$41,195,000	+$1,281,000
Other than full-time permanent	9,846,000	10,213,000	+367,000
Other personnel compensation	2,232,000	2,313,000	+81,000
Special personnel services	4,347,000	4,508,000	+161,000
Total, Personnel Compensation	56,339,000	58,229,000	+1,890,000
Personnel Benefits:			
Civilian personnel benefits	13,337,000	13,707,000	+370,000
Benefits for former personnel	116,000	34,000	-82,000
Travel and transportation of persons	2,817,000	2,894,000	+77,000
Transportation of things	428,000	420,000	-8,000
Rental Payments to GSA	1,335,000	1,373,000	+38,000
Rental payments to others	525,000	545,000	+20,000
Communications, utilities, and miscellaneous charges	3,579,000	3,668,000	+89,000
Printing and reproduction	901,000	921,000	+20,000
Consulting services	4,846,000	4,766,000	-80,000
Other services	63,198,000	65,201,000	+2,003,000
Purchases from Govt Accts	103,798,000	108,073,000	+4,275,000
Operation of GOCOs	28,527,000	28,477,000	-50,000
R&D Contracts	238,511,000	249,876,000	+11,365,000
Supplies and materials	24,539,000	25,313,000	+774,000
Equipment	9,083,000	9,509,000	+426,000
Lands and structures			
Grants, subsidies, and 'contributions	783,702,000	834,669,000	+50,967,000
Insurance claims and 'indemnities			
Interest and dividends	145,000	149,000	+4,000
Total Obligations	1,335,726,000	1,407,824,000	+72,098,000

DHHS–NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
Budget Authority by Object
including
Service and Supply
and Management Funds

	FY 1995 Current Estimate	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full–time permanent	$642,816,000	$665,091,000	+$22,275,000
Other than full–time permanent	117,865,000	122,147,000	+4,282,000
Other personnel compensation	37,721,000	39,272,000	+1,551,000
Special personnel services	72,535,000	75,329,000	+2,794,000
Total, Personnel Compensation	870,937,000	901,839,000	+30,902,000
Personnel Benefits:			
Civilian personnel benefits	184,534,000	190,951,000	+6,417,000
Benefits for former personnel	2,964,000	2,302,000	−662,000
Travel and transportation of persons	20,300,000	21,257,000	+957,000
Transportation of things	4,601,000	4,747,000	+146,000
Rental Payments to GSA	5,590,000	5,705,000	+115,000
Rental payments to others	101,228,000	104,889,000	+3,661,000
Communications, utilities, and miscellaneous charges	9,603,000	8,900,000	−703,000
Printing and reproduction	19,764,000	20,222,000	+458,000
Consulting services	18,647,000	21,052,000	+2,405,000
Other services	500,207,000	554,550,000	+54,343,000
Purchases from Govt Accts	203,350,000	214,223,000	+10,873,000
Operation of GOCOs	71,594,000	71,596,000	+2,000
R&D Contracts	817,568,000	850,747,000	+33,179,000
Supplies and materials	168,337,000	173,760,000	+5,423,000
Equipment	92,049,000	95,236,000	+3,187,000
Lands and structures	26,000	26,000	---
Grants, subsidies, and contributions	8,212,382,000	8,529,179,000	+316,797,000
Insurance claims and indemnities	1,704,000	1,724,000	+20,000
Interest and dividends	161,000	161,000	---
Total Obligations	11,305,546,000	11,773,066,000	+467,520,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
NIH TOTAL

Personnel Compensation & Administrative Cost

	FY 1995 Appropriation	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$450,751,000	$463,270,000	+$12,519,000
Other than full-time permanent	106,383,000	110,179,000	+3,796,000
Other personnel compensation	22,792,000	23,571,000	+779,000
Special personnel services	71,165,000	73,896,000	+2,731,000
Total, personnel compensation	651,091,000	670,916,000	+19,825,000
Civilian personnel benefits	137,956,000	141,917,000	+3,961,000
Benefits for former personnel	2,260,000	1,584,000	-676,000
Travel and transportation of persons	19,080,000	19,899,000	+819,000
Transportation of things	3,731,000	3,852,000	+121,000
Rental payments to others	4,576,000	4,735,000	+159,000
Communications, utilities, and miscellaneous charges	43,288,000	44,404,000	+1,116,000
Printing and reproduction	17,053,000	17,734,000	+681,000
Consulting services	13,392,000	15,850,000	+2,458,000
Other services	244,015,000	260,528,000	+16,513,000
Purchases from Govt Accts	524,598,000	544,763,000	+20,165,000
Operation of GOCOs	12,363,000	12,498,000	+135,000
Supplies and materials	127,496,000	130,577,000	+3,081,000
TOTAL NIH	1,800,899,000	1,869,257,000	+68,358,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
NON- AIDS

Personnel Compensation & Administrative Cost

	FY 1995 Appropriation	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$410,837,000	$422,075,000	+$11,238,000
Other than full-time permanent	96,537,000	99,966,000	+3,429,000
Other personnel compensation	20,560,000	21,258,000	+698,000
Special personnel services	66,818,000	69,388,000	+2,570,000
Total, personnel compensation	594,752,000	612,687,000	+17,935,000
Personnel Benefits:			
Civilian personnel benefits	124,619,000	128,210,000	+3,591,000
Benefits for former personnel	2,144,000	1,550,000	-594,000
Travel and transportation of persons	16,263,000	17,005,000	+742,000
Transportation of things	3,303,000	3,432,000	+129,000
Rental payments to others	4,051,000	4,190,000	+139,000
Communications, utilities, and miscellaneous charges	39,709,000	40,736,000	+1,027,000
Printing and reproduction	16,152,000	16,813,000	+661,000
Consulting services	9,346,000	11,884,000	+2,538,000
Other services	180,837,000	195,380,000	+14,543,000
Purchases from Govt Accts	438,263,000	454,338,000	+16,075,000
Operation of GOCOs	12,313,000	12,498,000	+185,000
Supplies and materials	102,957,000	105,264,000	+2,307,000
Total, NIH	1,544,709,000	1,603,987,000	+59,278,000

DHHS-NATIONAL INSTITUTES OF HEALTH

1996 CONGRESSIONAL JUSTIFICATION
AIDS

Personnel Compensation & Administrative Cost

	FY 1995 Appropriation	FY 1996 Estimate	Increase/ Decrease
Personnel Compensation:			
Full-time permanent	$39,914,000	$41,195,000	+$1,281,000
Other than full-time permanent	9,846,000	10,213,000	+367,000
Other personnel compensation	2,232,000	2,313,000	+81,000
Special personnel services	4,347,000	4,508,000	+161,000
Total, personnel compensation	56,339,000	58,229,000	+1,890,000
Personnel Benefits:			
Civilian personnel benefits	13,337,000	13,707,000	+370,000
Benefits for former personnel	116,000	34,000	-82,000
Travel and transportation of persons	2,817,000	2,894,000	+77,000
Transportation of things	428,000	420,000	-8,000
Rental payments to others	525,000	545,000	+20,000
Communications, utilities, and miscellaneous charges	3,579,000	3,668,000	+89,000
Printing and reproduction	901,000	921,000	+20,000
Consulting services	4,046,000	3,966,000	-80,000
Other services	63,178,000	65,148,000	+1,970,000
Purchases from Govt Accts	86,335,000	90,425,000	+4,090,000
Operation of GOCOs	50,000	0	-50,000
Supplies and materials	24,539,000	25,313,000	+774,000
Total, NIH	256,190,000	265,270,000	+9,080,000

NATIONAL INSTITUTES OF HEALTH

Justification

Management Fund

General Statement

The NIH Management Fund (MF) was established on June 29, 1957, by Public Law 85-67. The MF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The expenses for these activities are paid by the NIH appropriations and other government agencies. The services provided by the MF include utilities and plant maintenance, a 500 bed hospital and outpatient clinic, receipt, review and referral of research and training grant applications, collaborative computer science research and biomedical engineering, and general administrative support services.

The 1996 budget request for Computer Services increases by eighteen percent over 1995 due to the inclusion of $3,000,000 for communication infrastructure development.

NATIONAL INSTITUTES OF HEALTH

Management Fund

Obligations By Activity
(Dollars in thousands)

	1994 Actual FTEs	Amount	1995 Estimate FTEs	Amount	1996 Estimate FTEs	Amount
Computer Services..........	128	$19,849	123	$21,544	123	$25,347
Intramural scientific services.................	212	25,918	219	25,842	218	26,768
Clinical services..........	2,078	219,822	2,006	227,034	1,991	236,197
Grant review and approval.................	420	39,838	416	40,608	413	42,606
Intramural research support services.........	793	127,339	761	133,569	799	139,870
Rental payments............	---	23,133	---	26,414	---	27,192
Total Obligations..........	3,631	455,899	3,525	475,011	3,544	497,980

NATIONAL INSTITUTES OF HEALTH

Management Fund

Source of Income

	1994 Actual	1995 Estimate	1996 Estimate
NCI.............	$136,724,000	$138,605,000	$146,169,000
NHLBI...........	48,379,000	50,024,000	51,221,000
NIDR...........	9,337,000	8,567,000	9,782,000
NIDDK	28,642,000	28,364,000	28,274,000
NINDS...........	32,934,000	33,925,000	37,403,000
NIAID...........	33,455,000	33,155,000	36,855,000
NIGMS...........	7,903,000	7,699,000	8,186,000
NICHD...........	26,783,000	27,143,000	25,853,000
NEI.............	10,198,000	10,293,000	11,468,000
NIEHS...........	2,456,000	2,636,000	3,157,000
NIA.............	6,941,000	7,249,000	8,045,000
NIAMS...........	8,240,000	8,418,000	9,147,000
NIDCD...........	2,666,000	3,008,000	3,764,000
NIMH............	32,413,000	33,855,000	34,420,000
NIDA............	472,000	656,000	750,000
NIAAA...........	6,515,000	6,789,000	6,120,000
NCRR............	3,854,000	5,280,000	4,864,000
NINR............	1,066,000	1,003,000	1,207,000
NCHGR...........	2,027,000	5,915,000	6,491,000
FIC.............	1,177,000	1,359,000	1,448,000
NLM.............	9,293,000	9,238,000	10,122,000
FDA.............	6,032,000	7,098,000	7,401,000
SSF.............	10,573,000	10,957,000	11,003,000
SUBTOTAL	428,080,000	441,236,000	463,150,000
INTRAFUND BILLING.......	25,286,000	26,727,000	26,906,000
DIRECT REIMBURSEMENTS	2,533,000	7,048,000	7,924,000
	455,899,000	475,011,000	497,980,000

Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	56	55	55
Senior Grade	56	56	55
Full Grade	60	59	58
Senior Assistant Grade	27	27	27
Assistant Grade	24	23	23
Co-Step	3	3	3
Subtotal	227	224	222
Ungraded	311	297	293
Total Permanent Positions	3,552	3,487	3,458
Total Position, end of year	6,907	6,776	6,762
Total full-time equivalent (FTE) employment, end of year	3,631	3,525	3,544

Average ES Level	3.8	3.5	3.5
Average ES salary	$107,374	$108,582	$110,967
Average GS/GM grade	12.8	12.8	12.10
Average GS/GM salary	$51,278	$53,161	$56,184

CENTRAL SERVICES
Program Administration
Detail of End-of-Year Employment
Management Fund

	1994 Actual	1995 Estimate	1996 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
Total - Executive Level Salary			
ES-6	0	0	0
ES-5	1	2	2
ES-4	3	3	3
ES-3	2	2	2
ES-2	0	2	2
ES-1	0	0	0
Subtotal	6	9	9
Total - ES Salary	$644,395	$977,235	$998,703
GS/GM-15	84	79	81
GS/GM-14	196	188	188
GS/GM-13	187	189	196
GS-12	328	325	333
GS-11	365	352	353
GS-10	414	399	396
GS-9	218	213	213
GS-8	107	108	116
GS-7	287	281	275
GS-6	213	212	212
GS-5	225	222	221
GS-4	128	130	134
GS-3	34	36	37
GS-2	24	24	24
GS-1	1	1	1
Subtotal	2,811	2,759	2,780

NATIONAL INSTITUTES OF HEALTH

Management Fund

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	3,525	3,544	+19
Full-time equivalent of overtime and holiday hours	170	169	-1
Average ES salary	$108,582	$110,967	+$2,385
Average GM/GS grade	12.8	12.10	
Average GM/GS salary	53,161	56,184	+$3,023
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	62,991	65,604	2,613
Average salary of ungraded positions	30,675	31,906	1,231
Full-time permanent	$145,821,000	$153,571,000	+$7,750,000
Other than full-time permanent	10,309,000	10,732,000	+423,000
Other personnel compensation	11,493,000	11,985,000	+492,000
Special personnel services	1,370,000	1,433,000	+63,000
Subtotal Personnel Compensation	168,993,000	177,721,000	+8,728,000
Personnel benefits	37,181,000	39,200,000	+2,019,000
Benefits for former personnel	443,000	453,000	+10,000
Travel and transportation of persons ..	1,220,000	1,358,000	+138,000
Transportation of things	870,000	895,000	+25,000
Rent, communications and utilities	62,967,000	64,650,000	+1,683,000
Printing and reproduction	2,711,000	2,488,000	-223,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Other services	141,436,000	149,175,000	+7,739,000
Supplies and materials	40,129,000	42,309,000	+2,180,000
Equipment	19,061,000	19,731,000	+670,000
TOTAL	475,011,000	497,980,000	+22,969,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Justification

Service and Supply Fund

General Statement

The NIH Service and Supply Fund (SSF) was established on April 11, 1953, under 42 U.S.C. 231. The SSF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The SSF provides a single means for consolidating the financing and accounting of business-type operations involving the sales of services and commodities to customers. The services provided by the SSF include mainframe computing, engineering planning and design, printing, telecommunications, procurement, shipping and receiving, motor pool, research animals, fabrication and maintenance of scientific equipment, and other administrative support services.

The 1996 budget request for Other Services increases by nine percent due to increased patent prosecution contracting services and increased moving and warehouse services.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Budget Authority by Object

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	1,144	1,138	-6
Full-time equivalent of overtime and holiday hours	61	64	+3
Average ES salary	$109,336	$111,741	+$2,405
Average GM/GS grade	11.7	11.8	
Average GM/GS salary	$42,873	$44,622	+$1,749
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	61,077	63,000	1,923
Average salary of ungraded positions	37,266	38,647	1,381
Personnel compensation:			
Full-time permanent	$46,244,000	$48,250,000	+$2,006,000
Other than full-time permanent	1,173,000	1,236,000	+63,000
Other personnel compensation	3,436,000	3,716,000	+280,000
Special personnel services	---	---	---
Subtotal Personnel Compensation	50,853,000	53,202,000	+2,349,000
Personnel benefits	9,397,000	9,834,000	+437,000
Benefits for former personnel	261,000	265,000	+4,000
Travel and Transportation of persons ...	410,000	421,000	+11,000

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Transportation of things	588,000	664,000	+76,000
Rent, communications and utilities	33,685,000	35,504,000	+1,819,000
Printing and reproduction	5,098,000	5,176,000	+78,000
Other services	96,904,000	105,689,000	+8,785,000
Supplies and materials	51,323,000	52,792,000	+1,469,000
Equipment	18,713,000	19,201,000	+488,000
TOTAL	267,232,000	282,748,000	+15,516,000

Note: Includes FTEs associated with HIV Research Activities. Funds to report these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Obligations By Activity
(dollars in thousands)

	1994 Actual		1995 Estimate		1996 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Administrative Services:						
Cost of Goods Sold.......		$37,892		$41,472		$42,672
Other....................	788	141,231	808	146,332	807	158,105
Data processing services...	185	45,495	169	46,830	166	48,321
Instrumentation:						
Cost of Goods Sold.......		5,149		5,149		5,309
Other....................	62	7,470	68	7,768	67	8,033
Research animals...........	90	17,616	99	19,681	98	20,308
Total Obligations..........	1,125	254,853	1,144	267,232	1,138	282,748

CENTRAL SERVICES
Program Administration
Detail of End-of-Year Employment
Service and Supply Fund

	1994 Actual	1995 Estimate	1996 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
Total - Executive Level Salary			
ES-6	0	0	0
ES-5	0	0	0
ES-4	2	2	2
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	2	2	2
Total - ES Salary	$211,850	$218,672	$223,482
GS/GM-15	24	27	25
GS/GM-14	65	62	61
GS/GM-13	120	118	117
GS-12	144	145	141
GS-11	98	97	96
GS-10	3	3	3
GS-9	74	74	72
GS-8	34	31	31
GS-7	99	96	92
GS-6	62	61	59
GS-5	72	68	67
GS-4	44	46	44
GS-3	10	10	10
GS-2	0	0	0
GS-1	0	0	0
Subtotal	849	838	818

Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	1	1	1
Senior Grade	4	5	5
Full Grade	2	2	2
Senior Assistant Grade	3	5	5
Assistant Grade	0	0	0
Subtotal	10	13	13
Ungraded	219	237	236
Total Permanent Positions	1,137	1,153	1,132
Total Position, end of year	2,217	2,243	2,201
Total full-time equivalent (FTE) employment, end of year	1,125	1,144	1,138

Average ES Level	4.0	4.0	4.0
Average ES salary	$105,925	$109,336	$111,741
Average GS/GM grade	10.9	11.7	11.8
Average GS/GM salary	$39,538	$42,873	$44,622

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

FY 1996 Budget	Page No.
Appropriation language	166
Amounts available for obligation	167
Budget mechanism table	170
Summary of changes	172
Budget authority by Institute, Center, and Division	175
Budget authority by functional category	176
Budget authority by the comprehensive plan	178
Budget authority by object	179
Administrative costs	180
Significant Items in the House and Senate Appropriations Committee Reports	181
Authorizing legislation	184
Appropriation history	185
Budget authority history	186
Justification:	
A. General Statement	187
B. Research Program	190
C. FY 1996 Objectives in the comprehensive plan	202

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research
(INCLUDING TRANSFER OF FUNDS)

For carrying out Part D of Title XXIII of the Public Health Service Act, [$1,337,606,000] $1,407,824,000: Provided, That the Director of the Office of AIDS Research shall transfer from this appropriation the amounts necessary to carry out subsection 2353(d) of the Act.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995 P.L. 103.333.)

Office of AIDS Research

Amounts Available for Obligation

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation.........	---	$1,337,606,000	$1,407,824,000
Section 205 Procurement reduction......	---	-1,813,000	---
Section 207 Rent reduction...........	---	-5,000	---
Section 513 S&E reduction.............	---	-367,000	---
Subtotal, Adjusted appropriation.....	---	1,335,421,000	1,407,824,000
Comparative transfers from:			
National Cancer Institute...........	$213,017,000	---	---
National Heart, Lung, and Blood Institute.	54,977,000	---	---
National Institute of Dental Research.....	12,185,000	---	---
National Institute of Diabetes and Digestive and Kidney Diseases.....	10,437,000	---	---
National Institute of Neurological Disorders and Stroke	22,113,000	---	---
National Institute of Allergy and Infectious Diseases.	542,912,000	---	---
National Institute of General Medical Sciences...........	23,943,000	---	---
National Institute of Child Health and Human Development...	56,426,000	---	---
National Eye Institute	8,381,000	---	---

	1994 Actual	1995 Appropriation	1996 Estimate
National Institute of Environmental Health Sciences............	$5,608,000	---	---
National Institute on Aging...............	1,686,000	---	---
National Institute of Arthritis and Musculoskeletal and Skin Diseases.......	1,501,000	---	---
National Institute on Deafness and Other Communication Disorders...........	849,000	---	---
National Institute of Mental Health.......	87,182,000	---	---
National Institute on Drug Abuse..........	143,376,00	---	---
National Institute of Alcohol Abuse and Alcoholism..........	9,457,000	---	---
National Institute of Nursing Research....	4,229,000	---	---
National Center for Research Resources..	61,383,000	---	---
National Center for Human Genome Research............	637,000	---	---
John E. Fogarty International Center for Advanced Study in the Health Sciences.	8,852,000	---	---
National Library of Medicine............	2,782,000	---	---
Office of the Director	15,700,000	---	---

	1994 Actual	1995 Appropriation	1996 Estimate
Office of AIDS Research Discretionary Fund........	$8,838,000	---	---
Comparative transfer from Other NIH Institutes for Management Fund adjustment........	---	$305,000	---
Subtotal, adjusted budget authority...	1,296,471,000	1,335,726,000	$1,407,824,000
Unobligated balance, available start of year............	21,419,000	18,413,000	---
Unobligated balance, available end of year............	-18,413,000	---	---
Unobligated balance lapsing............	-332,000	---	---
Total, obligations..	1,299,155,000	1,354,139,000	1,407,824,000

NATIONAL INSTITUTES OF HEALTH

AIDS Budget Mechanism

Research Grants:	1994 Actual No.	1994 Actual Amount	1995 Appropriation No.	1995 Appropriation Amount	1996 Estimate No.	1996 Estimate Amount
Research projects:						
Noncompeting	1,064	$395,398,000	1,240	$450,287,000	1,317	$457,554,000
Administrative supplements	(64)	4,676,000	(40)	4,114,000	(40)	4,280,000
Competing projects:						
Renewals	158	45,131,000	153	42,170,800	151	59,190,300
New	433	114,331,000	321	86,700,200	267	101,426,700
Supplemental	5	1,255,000	9	2,174,000	13	3,200,000
Subtotal, competing	596	160,717,000	483	131,045,000	431	163,817,000
SBIR/STTR	44	6,779,000	91	14,023,000	101	17,451,000
Subtotal, research projects	1,704	567,570,000	1,814	599,469,000	1,849	643,102,000
Research Centers:						
Specialized/comprehensive	33	51,807,000	34	56,404,000	34	57,557,000
General Clinical Research	--	29,685,000	--	31,661,000	--	33,661,000
Biomedical research technology	--	854,000	--	854,000	--	1,854,000
Comparative medicine program	11	21,998,000	11	22,605,000	11	22,685,000
Biological models and materials research	--	248,000	--	250,000	--	250,000
Research centers in minority institutions	--	5,539,000	--	6,237,000	--	6,672,000
	44	110,131,000	45	118,011,000	45	122,679,000
Other Research:						
Research career programs	119	10,216,000	123	10,601,000	126	11,438,000
Cancer education	--	---	--	---	--	---
Cooperative clinical research	15	13,877,000	15	15,143,000	15	15,443,000
Biomedical research support	1	659,000	--	659,000	--	1,659,000
Minority biomedical research support	--	416,000	--	428,000	--	457,000
Other research	75	14,544,000	67	14,726,000	67	15,087,000
Subtotal, other research	210	39,712,000	205	41,557,000	208	44,084,000
Total, research grants	1,958	717,413,000	2,064	759,037,000	2,102	809,865,000

Research Training:						
Individual awards:						
Noncompeting	48	1,231,000	40	941,000	61	1,563,000
Competing projects	38	827,000	51	1,354,000	33	838,000
Subtotal, individual	86	2,058,000	91	2,295,000	94	2,401,000
Institutional awards:						
Noncompeting	462	11,796,000	571	14,665,000	556	14,667,000
Competing projects	209	5,742,000	94	3,041,000	113	3,436,000
Subtotal, institutional	671	17,538,000	665	17,706,000	669	18,103,000
Total, research training	757	19,596,000	756	20,001,000	763	20,504,000
Research and development contracts	285	279,784,000	294	277,317,000	290	288,880,000
SBIR/STTR	(4)	(283,000)	(1)	(766,000)	(4)	(682,000)
Intramural research		194,810,000		192,179,000		197,483,000
Research management and support		57,548,000		58,852,000		60,332,000
Subtotal, ICDs		1,269,151,000		1,307,386,000		1,377,064,000
National Library of Medicine		2,782,000		2,946,000		3,162,000
Office of the Director		24,538,000		25,394,000		27,598,000
Building and Facilities		---		---		---
TOTAL		1,296,471,000		1,335,726,000		1,407,824,000
Clinical Trials		(358,810,000)		(369,276,000)		(376,472,000)

Note: FTEs associated with HIV/AIDS Research activities are included in the justifications of the Institutes, Centers, and Divisions.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Summary of Changes

1995 Estimated budget authority	$1,335,726,000
1996 Estimated budget authority	1,407,824,000
Net change	+72,098,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increases		$44,713,000		+$639,000
b. One more day of pay		44,713,000		+177,000
c. Annualization of January 1995 locality pay increases		44,713,000		+336,000
d. January 1996 pay increases		44,713,000		+820,000
e. Increase in unemployment compensation		44,713,000		+8,000
f. Increased cost of centrally furnished services		50,259,000		+1,101,000
g. Increased cost of Service and Supply Fund		50,259,000		+619,000
h. Increased cost of laboratory supplies, materials, and other expenses		104,582,000		+2,711,000
i. DHHS Working Capital Fund		33,000		-1,000
j. FTS 2000 Reduction		157,000		-29,000
Subtotal				+6,381,000
2. Research management and support:				
a. Within grade increases		25,079,000		+369,000
b. One more day of pay		25,079,000		+96,000
c. Annualization of January 1995 locality pay raise		25,079,000		+176,000
d. January 1996 pay raise		25,079,000		+428,000
e. Increase in unemployment compensation		25,079,000		+2,000
f. Increased cost of centrally furnished services		6,986,000		+738,000
g. Increased cost of Service and Supply Fund		6,986,000		+232,000

Summary of Changes--continued

h. Increased cost of laboratory supplies, materials, and other expenses	20,574,000	+528,000
i. DHHS Working Capital Fund	648,000	-97,000
j. FTS 2000 Reduction	97,000	-17,000
Subtotal		+2,455,000
Subtotal		+8,836,000

	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	1,240	$454,401,000	+77	+$7,433,000
b. Competing	483	131,045,000	-52	+32,772,000
Subtotal	1,723	585,446,000	+25	+40,205,000
c. SBIR/STTR	91	14,023,000	+10	+3,428,000
Total	1,814	599,469,000	+35	+43,633,000
2. Research centers	45	118,011,000		+4,668,000
3. Other research	205	41,557,000	+3	+2,527,000
4. Research training	756	20,001,000	+7	+503,000
5. Research and development contracts	294	277,317,000	-4	+11,563,000
6. Intramural research		192,179,000		-1,077,000
7. Research management and support		58,852,000		-75,000
8. Office of AIDS Research		6,133,000		+1,520,000
Subtotal, program				+63,262,000
Total changes				+72,098,000

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of AIDS Research

FY 1996 Congressional Justification

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
NCI	$213,017,000	$218,504,000	$225,790,000
NHLBI	54,977,000	55,485,000	57,925,000
NIDR	12,185,000	11,745,000	12,309,000
NIDDK	10,437,000	10,752,000	11,735,000
NINDS	22,113,000	22,741,000	23,807,000
NIAID	542,912,000	558,411,000	596,018,000
NIGMS	23,943,000	24,664,000	26,135,000
NICHD	56,426,000	58,667,000	60,713,000
NEI	8,381,000	8,633,000	9,125,000
NIEHS	5,608,000	5,745,000	6,051,000
NIA	1,686,000	1,715,000	1,785,000
NIAMS	1,501,000	2,879,000	3,039,000
NIDCD	849,000	1,552,000	1,650,000
NIMH	87,182,000	89,435,000	93,556,000
NIDA	143,376,000	147,402,000	153,331,000
NIAAA	9,457,000	9,741,000	10,135,000
NINR	4,229,000	4,577,000	4,896,000
NCRR	61,383,000	64,630,000	68,370,000
NCHGR	637,000	1,000,000	1,000,000
FIC	8,852,000	9,108,000	9,694,000
Subtotal	1,269,151,000	1,307,386,000	1,377,064,000
NLM	2,782,000	2,946,000	3,162,000
OD	24,538,000	25,394,000	27,598,000
B&F	—	—	—
TOTAL	1,296,471,000	1,335,726,000	1,407,824,000

DHHS–National Institutes of Health
AIDS By Functional Category

Category	FY 1994 Actual Budget Authority	FY 1995 Appropriation	FY 1996 President's Budget
I. BASIC SCIENCE RESEARCH:			
A. Biomedical Research:			
1. HIV and HIV genome	$104,116,000	$117,946,000	$130,614,000
2. Immunology	133,862,000	130,576,000	142,764,000
3. Blood/Blood products	10,866,000	23,434,000	18,223,000
4. Diagnostic methods/reagents development	8,758,000	8,333,000	8,749,000
5. Animal models and related studies	35,081,000	35,865,000	37,988,000
SUBTOTAL, Biomedical Research	292,683,000	316,154,000	338,338,000
B. Neuroscience and Neuropsychiatric Research	48,440,000	50,482,000	52,734,000
C. Behavioral Research:			
1. Mechanisms of behavior and behavior change	25,842,000	27,813,000	28,133,000
2. Prevention of high–risk behaviors	131,574,000	134,453,000	137,958,000
SUBTOTAL, Behavioral Research	157,416,000	162,266,000	166,091,000
D. Therapeutic Agents:			
1. Development	182,966,000	192,585,000	204,219,000
2. Clinical Trials	281,609,000	287,026,000	292,123,000
SUBTOTAL, Therapeutic Agents	464,575,000	479,611,000	496,342,000
E. Vaccines:			
1. Development	77,266,000	82,736,000	88,305,000
2. Clinical Trials	42,277,000	39,878,000	44,374,000
SUBTOTAL, Vaccines	119,543,000	122,614,000	132,679,000
F. Research Enhancement:			
1. Training	23,608,000	24,903,000	25,885,000
2. Construction (Extramural)			
SUBTOTAL, Research Enhancement	23,608,000	24,903,000	25,885,000
TOTAL, BASIC SCIENCE RESEARCH	1,106,265,000	1,156,030,000	1,212,069,000
II. RISK ASSESSMENT AND PREVENTION:			
A. Surveillance:			
1. Diseases associated with HIV	750,000	987,000	1,016,000
2. HIV surveys (incidence, prevalance)	1,606,000	2,232,000	2,033,000
3. Knowledge, attitudes, behaviors	1,491,000	2,377,000	2,600,000
SUBTOTAL, Surveillance	3,847,000	5,596,000	5,649,000
B. Population–Based Research: Natural History, Transmission, Risk Factors:			
1. Transmission:			
a. Sexual	23,668,000	23,744,000	24,890,000
b. Intravenous drug abusers	1,551,000	1,610,000	2,037,000
c. Hemophilia populations	2,138,000	1,843,000	1,923,000
d. Blood recipient/donor studies	8,706,000	3,225,000	5,983,000
e. Perinatal infection	35,713,000	28,319,000	32,912,000
f. Occupationally related	226,000	237,000	247,000
g. Other/Miscellaneous	7,553,000	7,384,000	7,587,000
SUBTOTAL, Transmission	79,555,000	66,362,000	75,579,000
2. Natural history and cofactors	94,281,000	95,367,000	101,977,000
SUBTOTAL, Population based research	173,836,000	161,729,000	177,556,000

Category	Actual Budget Authority	FY 1995 Appropriation	FY 1996 President's Budget
C. Information and Education/Preventive Services:			
1. High risk or infected persons:			
a. Health education/risk education	531,000	624,000	626,000
b. Counseling, testing, partner notification	98,000	99,000	103,000
c. Perinatal AIDS prevention projects			
d. HIV prevention among drug abusers	1,735,000	1,900,000	2,000,000
e. Special projects:			
(1) Conference of Mayors			
(2) HIV-related tuberculosis demonstration projects			
(3) National Hemophilia AIDS/HIV prevention project			
(4) Community-based demonstration projects			
SUBTOTAL, Special projects			
SUBTOTAL, High-Risk or Infected Persons	2,364,000	2,623,000	2,729,000
2. Special Minority Initiatives			
3. School and college aged youth:			
a. National efforts			
b. State and local projects			
c. Program development and training			
SUBTOTAL, School and college aged youth			
4. General Public and Special Programs:			
a. National:			
(1) Clearinghouse			
(2) Hotline (general public)			
(3) Treatment trials and therapy, information services	4,213,000	4,256,000	4,527,000
SUBTOTAL, National	4,213,000	4,256,000	4,527,000
b. Regional, state, and local	223,000	232,000	252,000
SUBTOTAL, Gen. Pub. and Spec. Prog.	4,436,000	4,488,000	4,779,000
5. Health-Care Workers and Providers:			
a. Education and training centers	741,000	723,000	717,000
b. Other types of training	856,000	519,000	539,000
SUBTOTAL, Health-Care Workers and Providers	1,597,000	1,242,000	1,256,000
6. Prevention Capacity Enhancement			
SUBTOTAL, Information and education/preventive services	8,397,000	8,353,000	8,764,000
TOTAL, RISK ASSESSMENT AND PREVENTION......	186,080,000	175,678,000	191,969,000
IV. CLINICAL HEALTH SERVICES RESEARCH AND DELIVERY:			
A. Services			
B. Health Services Grants			
C. Construction			
D. Research	4,126,000	4,018,000	3,786,000
TOTAL, CLINICAL HLTH SERV. RESCH AND DEL.	4,126,000	4,018,000	3,786,000
V. PHS-WIDE ACTIVITIES:			
C. Construction (PHS Faciltites)			
TOTAL................................	1,296,471,000	1,335,726,000	1,407,824,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Funding by the FY 1996 Comprehensive Plan

Area of Emphasis	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
Natural History and Epidemiology	$176,002,000	$177,981,000	$188,111,000
Etiology and Pathogenesis	333,565,000	345,436,000	375,010,000
Therapeutics	456,052,000	473,523,000	495,507,000
Vaccines	109,992,000	111,631,000	118,066,000
Behavioral Research	157,498,000	159,521,000	161,224,000
Training and Infrastructure	38,876,000	40,846,000	42,448,000
Information Dissemination	15,648,000	16,788,000	17,458,000
OAR Discretionary Fund	8,838,000	10,000,000	10,000,000
TOTAL FUNDING BY THE PLAN	1,296,471,000	1,335,726,000	1,407,824,000

National Institutes of Health

Office of AIDS Research

Budget Authority by Object

	Object Class	FY 1995 Appropriation	FY 1996 Estimate	Change
	Personnel Compensation:			
11.1	Full-time permanent	$39,914,000	$41,195,000	+$1,281,000
11.3	Other than full-time permanent	9,846,000	10,213,000	+367,000
11.5	Other personnel compensation	2,232,000	2,313,000	+81,000
11.8	Special personal services payments	4,347,000	4,508,000	+161,000
11.9	Total, Personnel Compensation	56,339,000	58,229,000	+1,890,000
12.1	Civilian personnel benefits	13,337,000	13,707,000	+370,000
13.0	Benefits for former personnel	116,000	34,000	-82,000
21.0	Travel and transportation of persons	2,817,000	2,894,000	+77,000
22.0	Transportation of things	428,000	420,000	-8,000
23.1	Rental payment to GSA	1,335,000	1,373,000	+38,000
23.2	Rental payments to others	525,000	545,000	+20,000
23.3	Communications, utilities, and miscellaneous charges	3,579,000	3,668,000	+89,000
24.0	Printing and reproduction	901,000	921,000	+20,000
25.1	Consulting services	4,846,000	4,766,000	-80,000
25.2	Other services	63,198,000	65,201,000	+2,003,000
25.3	Purchases from govt. accounts	103,798,000	108,073,000	+4,275,000
25.4	Operation of GOCOs	28,527,000	28,477,000	-50,000
25.5	Research and development contracts	238,511,000	249,876,000	+11,365,000
26.0	Supplies and materials	24,539,000	25,313,000	+774,000
31.0	Equipment	9,083,000	9,509,000	+426,000
41.0	Grants, subsidies, and contributions	783,702,000	834,669,000	+50,967,000
43.0	Interest and dividends	145,000	149,000	+4,000
99.9	TOTAL, NIH	1,335,726,000	1,407,824,000	+72,098,000

National Institutes of Health

Office of AIDS Research

Administrative Costs

	Object Class	FY 1995 Appropriation	FY 1996 Estimate	Change
	Personnel Compensation:			
11.1	Full-time permanent	$39,914,000	$41,195,000	+$1,281,000
11.3	Other than full-time permanent	9,846,000	10,213,000	+367,000
11.5	Other personnel compensation	2,232,000	2,313,000	+81,000
11.8	Special personal services payments	4,347,000	4,508,000	+161,000
11.9	Total, Personnel Compensation	56,339,000	58,229,000	+1,890,000
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25.2	Other services	63,198,000	65,201,000	+2,003,000
25.3	Purchases from govt. accounts	103,798,000	108,073,000	+4,275,000
25.4	Operation of GOCOs	28,527,000	28,477,000	-50,000
26.0	Supplies and materials	24,539,000	25,313,000	+774,000
99.9	TOTAL, NIH	302,950,000	312,248,000	+9,080,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1995 House Report	
Center Grants	
1. "For some time, NIH has funded AIDS center grants to encourage collaboration among investigators at major research institutions. It is the Committee's understanding that, of the top fifteen institutions receiving AIDS research funding, only six have applied and been granted center awards. The Committee encourages OAR to further consider ways in which programs can be developed to encourage active inter-disciplinary, team oriented collaboration among researchers at institutions receiving the highest level of AIDS funding." (page 71)	1. The OAR has placed a priority on supporting investigator-initiated research, encouraging investigators with innovative approaches to participate in AIDS research, and facilitating collaborations between AIDS researchers to further the basic scientific understanding of the disease. Such collaborations can provide crucial information on HIV and its immunopathogenesis that is necessary to develop improved therapeutic regimens, vaccines, and behavioral modifications to treat, prevent and control HIV infection and its sequelae. Center grants, such as the NIAID-sponsored Centers for AIDS Research (CFAR), represent highly specialized awards to institutions with significant impact on the conduct of HIV-related research. The CFAR program encourages collaboration among AIDS researchers in diverse research fields including virology, immunology, microbiology, molecular biology, and animal models and provides a "core" of shared facility resources and technical support. With these issues in mind the OAR is considering how best to meet the needs of interdisciplinary collaboration among researchers at institutions across the country.

Item	Action Taken or To Be Taken
Perinatal transmission	
2. "The Committee is encouraged by the preliminary results of the recent NIH clinical trial which shows dramatic reductions in the rates of perinatal transmission of AIDS when AZT is administered to mothers. The Committee urges NIH to undertake joint programs with HRSA to support coordination of care and access to research to protocols for women." (page 71)	2. The Office of AIDS Research, as well as numerous ICDs of the NIH, will continue to actively work with other PHS agencies to help coordinate care and access to research protocols for women, adolescents, and children.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1995 Senate Report	
Transfer of funds	
1. "The bill includes an appropriation within this amount of $1,337,606,000 for AIDS research throughout NIH...These funds have been included in a single consolidated appropriation as requested by the President. The law provides that the funds will be transferred within 30 days after enactment of the appropriations bill to the Institutes and centers. The Committee expects to be consulted prior to the execution of these transfers if the allocations differ significantly from the distribution among Institutes described in the 1995 budget justifications." (page 119)	1. The Office of AIDS Research will consult with the Committee prior to the execution of the transfer of moneys to the Institutes and Centers if the allocations differ significantly from the levels described in the FY 1995 budget justifications.
Perinatal Transmission	
2. The Committee understands that further studies are needed to determine which components of AZT administration are the most effective in reducing perinatal transmission and encourages the OAR to work with HRSA, the CDC, and grantees under title IV of the Ryan White Act to help coordinate care and access to research protocols for women, youth, and children. (page 119)	2. Same as House Report Number 2.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation..	Title IV Section 301		Indefinite	$1,305,725,000	Indefinite	$1,377,320,000
Office of AIDS Research.......	Title XXIII Section 2351			---		
Emergency Discretionary Fund...	Title XXIII Section 2356		$100,000,000	10,000,000	$100,000,000	10,000,000
National Research Service Awards..	Section 487(d)		Such sums as necessary	20,001,000	Such sums as necessary	20,504,000
				1,335,726,000		1,407,824,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Appropriation History

Year	Budget Estimate 1/ to Congress	House Allowance	Senate Allowance	Appropriation
1995	$1,379,052,000	$1,337,606,000	$1,337,606,000	$1,335,421,000 2/
1996	$1,407,824,000			

1/ Includes all amounts associated with the National Institutes of Health AIDS Research Program.

2/ Excludes procurement reform, rent, and salary and expense reductions of $2,185,000.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Budget Authority
(Dollars in thousands)

FY 1992	1,047,456
FY 1993	1,071,457
FY 1994	1,296,471
FY 1995	1,335,726
FY 1996	1,407,824

Note: FTEs associated with HIV/AIDS Research Activities are found in the Institutes, Centers, and Divsions.

Justification

Office of AIDS Research

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$1,296,471,000	$1,335,726,000	$1,407,824,000	+$72,098,000

General Statement

The National Institutes of Health (NIH) have made major contributions to the basic understanding and therapeutic management of all stages and manifestations of HIV infection and AIDS. With so many Americans dying of AIDS, there is an urgent need to advance these efforts and stem the human, societal, and economic losses due to this pandemic.

As AIDS and AIDS-related scientific endeavors enter the second decade, the spectrum of HIV infection also has broadened in new directions. Disparate and aggressive AIDS-related malignancies and opportunistic infections (OIs) have increased significantly. HIV infection rates also have increased significantly among minorities, women, children, adolescents, and injecting drug users (IDUs). Such populations have different risks for infection, exhibit some different clinical manifestations, and often have complex socioeconomic issues related to their HIV infection. These areas of emerging challenge are of major importance to society and the NIH.

AIDS-related research is continuing to be a rapidly developing scientific field of investigation involving various scientific disciplines. The primary goal of the NIH is to support basic biomedical research for the identification and development of new therapeutic drugs and vaccines that can extend the life span and quality of life of HIV-infected individuals and prevent non-infected individuals from contracting the disease. To achieve this, in FY 1996 the NIH is dedicated to supporting and accelerating research on all five areas of AIDS research with particular emphasis on expanding unsolicited investigator initiated research on: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral Research. The NIH will also focus on enhancing these efforts through training and infrastructure development and improving the dissemination of critical information that results from NIH-sponsored AIDS research.

various phases of cell development. These drugs may be able to inhibit HIV replication and restore functional immune systems and prevent the OIs and malignancies associated with HIV infection.

IV. Vaccines

The FY 1996 Estimate for Vaccines Research is $118,066,000 an increase of $6,435,000 or 5.8 percent over the FY 1995 Appropriation of $111,631,000. The NIH will continue research on the development of potential vaccines, including genetically-engineered vaccines such as synthetic peptide and non-infectious particles capable of producing long-term protection from mucosal, intravenous, and perinatal--mother-to-child--transmission as well as disease progression in HIV-infected individuals.

V. Behavioral Research

The FY 1996 Estimate for Behavioral Research is $161,224,000 an increase of $1,703,000 or 1.0 percent over the FY 1995 Appropriation of $159,521,000. Efforts to determine the spectrum and frequency of behaviors associated with risk of HIV transmission among various regional and demographic subpopulations as well as within the general population are under investigation.

VI. Training and Infrastructure

The FY 1996 Estimate for Training and Infrastructure is $42,448,000 an increase of $1,602,000 or 3.9 percent over the FY 1995 Appropriation of $40,846,000. The NIH will continue to expand training of domestic and foreign biomedical and behavioral researchers to conduct AIDS related-research.

VII. Information Dissemination

The FY 1996 Estimate for Information Dissemination is $17,458,000 an increase of $670,000 or 4.0 percent over the FY 1995 Appropriation of $16,788,000. Efforts to disseminate state-of-the-art clinical findings as well as health care and prevention information to domestic and international audiences will continue.

Overall Budget Policy

The President's Appropriation request of $1,407,824,000 represents current law requirements. No proposed law amounts are included. Funding for the Office of AIDS Research during the last five years has been as follows:

	Amount
FY 1991	$1,012,469
FY 1992	1,047,456
FY 1993	1,071,457
FY 1994	1,296,471
FY 1995	1,335,726

Purpose and Method of Operation

The OAR and the NIH Institutes and Centers worked together to develop and implement the FY 1996 comprehensive plan for HIV-related research, setting forth the total NIH research effort for this disease and its sequelae. Through the planning process, which included experts from many areas of science as well as community representatives, an unprecedented consensus has developed that NIH must rededicate our research efforts to understanding the basic biology of the virus, of its mode of establishing infection, of the pathogenesis of the disease, and of the causes of HIV-associated immunodeficiency. The scientific insight and expertise gained from AIDS-related research will be utilized to resolve a wide spectrum of other basic scientific issues in the fields of virology, immunology, microbiology, molecular biology, oncology, and animal models, which will benefit non-AIDS research areas as well.

Specific plans for each of the seven areas are as follows:

I. Natural History and Epidemiology

The FY 1996 Estimate for Natural History and Epidemiology Research is $188,111,000 an increase of $10,130,000 or 5.7 percent over the FY 1995 Appropriation of $177,981,000. The NIH is focusing its research on factors and cofactors related to all modes of transmission and the natural history of HIV infection in affected populations with emphasis on women, children, adolescents, minorities, and IDUs.

II. Etiology and Pathogenesis

The FY 1996 Estimate for Etiology and Pathogenesis Research is $375,010,000 an increase of $29,574,000 or 8.6 percent over the FY 1995 Appropriation of $345,436,000. NIH initiatives include basic research on understanding how the virus infects the cell and understanding its life cycle and the immune response to the virus.

III. Therapeutics

The FY 1996 Estimate for Therapeutics Research is $495,507,000 an increase of $21,984,000 or 4.6 percent over the FY 1995 Appropriation of $473,523,000. NIH-sponsored studies are actively pursuing the drug screening and rational targeted drug programs. Targeted drugs are designed to interrupt

AIDS Research

The FY 1996 budget request symbolizes a turning point in the conduct of AIDS research. It is based on a frank assessment of our successes and failures and charts a new course for the future. It also represents the opportunity for the NIH to set in place refocused scientific priorities and to shift resources to meet these priorities.

The NIH Revitalization Act restructured the way the NIH carries out AIDS research, investing primary responsibility for planning, coordinating, and funding of all AIDS-related research in the Office of AIDS Research. The OAR invited distinguished scientists, both from within the world of AIDS research and from related disciplines, to join in crafting a new program for AIDS research. The process was unique and inclusive, involving the NIH Institute and Center Directors; NIH intramural and extramural scientists and program managers; scientists and researchers from other government agencies, academia, foundations, and industry; HIV-infected men and women; and other community representatives. This diverse and eminent group of experts reached an unprecedented consensus regarding the priorities for HIV-related research, which is reflected in the *FY 1996 Plan for HIV-related Research* and in this FY 1996 request.

The HIV/AIDS Pandemic

More than 985,000 cases of AIDS have been reported to the World Health Organization (WHO) from more than 160 countries. Because of under-reporting, the actual number of people with AIDS is certainly much higher. As of July 1994, it has been estimated that the cumulative AIDS cases total 4 million and that 17 million individuals are infected with HIV. By the year 2000, it is expected that between 30 and 40 million people will have been infected with HIV. In the United States, one person dies of acquired immunodeficiency syndrome (AIDS) every 8 minutes. Approximately 1 million Americans are infected with HIV, and the number of HIV-infected individuals continues to increase.

In the U.S. and around the world, AIDS affects young individuals disproportionately. AIDS is now the leading cause of death in young men aged 25-44 in 64 U.S. cities. AIDS is also the leading cause of death among women in this age group in nine major cities. Although deaths among young adults made up only 7% of U.S. deaths from all causes in 1990, they are disproportionately disruptive to society. Persons aged 25-44 years constituted 54 percent of the U.S. civilian labor force in 1992. Such premature deaths result in the loss of many productive years of life and deprive young children of their parents.

The epidemic in the U.S. has undergone striking demographic changes. Homosexual men no longer represent the majority of new cases reported. CDC surveillance data show that in 1993 the rates of increases in AIDS cases were greatest for women, adolescents, persons infected through heterosexual contact, minorities, and injection drug users. In 1993, minorities represented more than half of the new cases of AIDS among men, more than 75 percent among women, and 84 percent among children. The risk of infection for an African-American woman was 15 times that of a white woman.

The changing character of the pandemic in the United States has led to a disproportionate increase in AIDS cases among women. As more women have become HIV-infected, there has been a concomitant increase in the number of pediatric cases. In some major urban areas, AIDS is among the five leading causes of death of children aged 1 to 4 years. The social and psychological costs are great, since many of these children have parents who are themselves HIV-infected or dying of AIDS and cannot care for them. While much attention has focused on the unique aspects of transmission and clinical manifestations of HIV infection in infants and children, the growing rate of HIV infection among adolescents (aged 10 to 18 years) has been recognized as a problem of both scientific and societal importance.

The NIH HIV-Related Research Program

The NIH has played a leadership role in the discovery and characterization of HIV and in research aimed at determining the pathogenesis of AIDS and in combating this dread disease. The NIH supports and conducts a comprehensive program of basic and clinical biomedical and behavioral research. To sustain such research, the NIH has initiated programs for the training of research personnel and for the development and maintenance of research resources, such as the primate research centers. The NIH has also developed programs for the collection, dissemination, and exchange of scientific and clinical information about AIDS.

The progress that has been made in identifying and understanding HIV and in unraveling the means through which infection results in AIDS, in the nature of the immunodeficiency that occurs, in the development of therapies for HIV and for opportunistic infections, and in the introduction of effective behavior modification strategies could only have been made because of the base of biomedical and behavioral research efforts that had anteceded the appearance of AIDS. This emphasizes the need for a very intimate interaction between AIDS-related research and general biomedical and behavioral research efforts. Studies of AIDS draw on the immense body of fundamental and clinical knowledge that has developed through NIH (and other) research support. Similarly, the effort to understand HIV and AIDS has led to, and will continue to result in, research strides that benefit research on many other diseases. Great advances in retrovirology and in the understanding of the human immune system that have emerged from studies of AIDS have immeasurably enriched our efforts to attack a large number of other human diseases of major importance. A balanced program of support for AIDS research and for biomedical research in general is essential if we are to make real progress against this disease.

Each NIH Institute, Center, and Division (ICD) is involved in some HIV/AIDS-related research activity, consistent with its individual mission. The Office of AIDS Research, within the Office of the Director, NIH, has overall responsibility to plan, coordinate, evaluate, and fund the AIDS research program of the NIH. The NIH HIV-related research effort is divided into five major scientific categories: (1) natural history and epidemiology, (2) etiology and pathogenesis, (3) therapeutics, (4) vaccines, and (5) behavioral research. These research programs are conducted both through the NIH-sponsored programs of grants and contracts at major universities, research institutes, and small science-oriented businesses and in the NIH intramural research programs, mainly located in Bethesda and Frederick, Maryland. Dividing the AIDS science effort by subject matter helps in research planning, but such subdivisions have not had the effect of insulating these fields of research from one another. Rather, these areas are inextricably linked and many research projects represent interdisciplinary approaches that deal with more than one of these areas. Similarly, although the extramural and intramural research efforts are supported by different funding mechanisms, they represent a single overall endeavor, and often intramural and extramural research groups collaborate on specific research projects. Two additional components provide important research resources to these efforts: training and infrastructure, and information dissemination.

Under the provisions of the NIH Revitalization Act of 1993, the OAR receives all funds available for AIDS activities of the National Institutes of Health. The Administration implements this provision of the Act by requesting a single appropriation for all AIDS research which the OAR distributes to the ICDs of the NIH based on the objectives and priorities of the comprehensive plan. This single appropriation allows the OAR to manage effectively the research resources on the basis of sound scientific judgment while taking advantage of the most promising scientific avenues. An OAR Discretionary Fund is also authorized to allow expeditious pilot funding for new scientific initiatives as well as rapid supplementary funding for scientific "breakthroughs" or emergencies in ongoing research.

Natural History and Epidemiology

The NIH performs epidemiologic research in which cohorts of HIV-infected individuals and healthy individuals who are at risk of infection are prospectively studied. A number of such epidemiologic studies aimed at examining the natural history of HIV infection and the effects of viral factors, host factors, cofactors, and therapeutic and prophylactic interventions on the risk of infection and disease progression are under way. This research is performed in the United States as well as in other countries that may exhibit different patterns of the epidemic. Such studies, therefore, provide unique opportunities for identifying risk factors, better understanding the natural history of HIV infection, and identifying populations suitable for participation in future domestic and international HIV drug and vaccine efficacy trials. Examples of such research include the study of sexual transmission in specific populations; the study of the natural history of HIV-related disease in women, men, adolescents, and children; the study of perinatal transmission; and the study of behavior relative to the risk of transmission of HIV.

Etiology and Pathogenesis

To prevent HIV infection and to combat HIV and AIDS in infected individuals, a sophisticated understanding of the viral life cycle, of the pathogenetic mechanisms leading to disease, of the immune response to HIV, and of the mechanisms responsible for immunodeficiency is essential. Examples of such research include the detailed characterization of the structure and function of each of the HIV-encoded proteins; the determination of the nature of the immune response to HIV and whether that response helps to control progression or, under certain circumstances, actually hastens development of disease; understanding of the mechanisms through which infection spreads throughout the body and how such infection results in immunodeficiency; determining how HIV-related malignancies develop and progress; understanding the development of neurological and neuropsychiatric complications; and elucidating the means through which wasting and endocrine disorders are mediated. The elucidation of cofactors that may play a role in the progression of AIDS and of complications that develop are priority subjects for study. The identification of genes that enhance or limit susceptibility to infection and/or to disease progression is of critical importance. Efforts to understand unique factors that determine susceptibility to infection, progression of infection, and unique clinical manifestations in women, children, and adolescents are receiving major attention.

Therapeutics

NIH-sponsored studies are actively pursuing the discovery and development of potential therapies for the prophylaxis, early intervention, and treatment of HIV infection and its sequelae. Two approaches are being taken for the identification of potential antiretroviral agents, including targeted drug development that utilizes structural biology techniques specifically to design drugs that interfere at various stages of the HIV life cycle, and drug screening of synthetic and natural products for anti-HIV activity. The NIH sponsors intramural and extramural clinical trials of these potential therapeutic agents in single- or multi-drug regimens to demonstrate drug safety and efficacy for the control and treatment of HIV infection and its accompanying opportunistic infections and malignancies in individuals of all ages. Innovative new therapies for immune reconstitution based on the use of cytokine and cytokine-related agents and on cellular replacement are receiving emphasis. A variety of gene therapy approaches to render cells resistant to HIV are being actively pursued.

Vaccines

The eradication of AIDS will ultimately depend upon the development of a safe, highly effective preventive vaccine. Based on the growing knowledge of viral gene products and the immune response to them, vaccine candidates are being developed. These potential vaccines and their congeners have been initially studied in primate and non-primate models for both safety and efficacy and are then utilized in trials in human volunteers. The determination of optimal modes of immunization, optimal adjuvants and co-factors, and the nature of the immunity that would be most effective are under very active study. Among the vaccine candidates under study and/or development are purified recombinant viral proteins, viral vectors such as avipox, into which key HIV genes have been cloned, whole killed viruses, and attenuated live virus. New modes of immunization, such as the use of viral subunit DNA, the development of novel adjuvants, and the use of cytokines as immunization cofactors are receiving major emphasis. Vaccine discovery and development efforts are being closely coordinated with U.S. and international epidemiology studies to identify genetic variations in HIV that may be important for the design of vaccines and to identify populations suitable for future efficacy trials. Special issues such as the use of vaccines to prevent maternal-fetal transmission and post-infection vaccination continue to receive emphasis.

Behavioral Research

The NIH conducts basic research on behavior and the means of motivating and sustaining behavior change. These efforts provide information that is relevant to the design of intervention programs aimed at reducing HIV transmission, including identification of effective approaches to modifying behavior and sustaining behavior change, identification of cultural barriers and enhancers to behavior change, and identification of populations resistant to behavior intervention. Some studies are international in scope, including a collaborative effort between the NIH and the U.S. Agency for International Development. Studies in other areas of behavioral research are determining how HIV-infected individuals are perceived and how individuals and their families respond to and cope with the disease and its manifestations. Behavioral research also supports the conduct of biomedical clinical trials by enhancing recruitment and protocol adherence.

Training and Infrastructure

The NIH supports a number of intramural and extramural research resource programs. Included in these programs are grants for training AIDS researchers, developing animal models, and constructing or improving existing facilities and equipment for AIDS research.

Information Dissemination

The NIH has addressed the important need for information dissemination in a number of arenas. Standards-of-care information requires coordination among various agencies of the Public Health Service (PHS) as well as outside organizations. The NIH supports several computerized databases as well as mechanisms such as the "Clinical Alerts" to rapidly disseminate critical clinical trials results to health professionals. Within its mission, the OAR strives to improve the dissemination of information to ensure that research findings are rapidly incorporated into treatment regimens used by health care professionals. To that end, the OAR supports a technology transfer program that focuses particular attention on disseminating research findings to community physicians and health providers in regions with limited access to state-of-the-art treatment information.

Scientific Opportunities and Priorities

Much progress has been made in the first decade of AIDS research. We have a better understanding of the molecular virology of HIV, a knowledge made possible by pioneering work in retrovirology and molecular biology conducted for two decades preceding the discovery of HIV. This work, while not yet matched in depth by our grasp of the means through which infection leads to disease and how it induces immune deficiency, has, nonetheless, provided us with unique insights into the virus. A class of useful antiretroviral drugs, the reverse transcriptase inhibitors, has been introduced. One of these agents, zidovudine (AZT), can dramatically reduce the risk of transmission of HIV infection from a pregnant women to her child. Effective treatments for HIV-related opportunistic infections can prolong and improve the lives of people living with AIDS. Yet, we lack an effective preventive vaccine, and classes of effective antiviral agents, in addition to the reverse transcriptase inhibitors, are critically needed. Our understanding of mechanisms to modify risk-taking behavior is still very limited. We do not yet understand many aspects of the interaction between the virus and the infected individual.

The FY 1996 planning process has made clear that the NIH must intensify efforts to understand, in detail, the mechanisms through which infection is established, how the disease propagates, what causes the profound immunodeficiency, and how the terrible complications of the disease are induced. Understanding the structure and function of both the viral and cellular proteins that are critical in infection, and possibly in cellular death, promises to provide targets for new generations of vaccines and for development of new therapeutic agents through rational drug design. The most important scientific opportunities lie in our insight into the virus and the disease that it causes.

The FY 1996 budget requests funds to support the critical areas of scientific opportunities, summarized in the following categories:

Basic Research

The engine that will drive forward the entire AIDS research enterprise is basic research. This budget request reflects the view that the current inadequacy of treatments for HIV infection and the absence of an effective vaccine to protect the uninfected are largely due to the wide gaps in our understanding of the pathogenesis of HIV disease, of the details of the viral life cycle and the function of the viral proteins, and of the interactions of the virus with the immune system.

The NIH will rededicate its efforts to basic research to meet these and other challenges. A vigorous program of creative investigator-initiated work is essential. Indeed, in the temptation to manage the research effort, it must be recalled that the pathbreaking work, which has the capacity to transform our approach to this disease, will come from insights that cannot be planned in any administrative office. Command science is no more likely to succeed than command economics. OAR will increase the resources available for support of investigator-initiated work and will use all of our powers to persuade a broader pool of basic scientists to join us in this effort.

Clinical Research

The largest investment of AIDS research dollars is in clinical research. The AIDS research program will actively support a balanced portfolio of both small, laboratory-intensive, pathogenesis-based studies and larger, longer studies that measure efficacy of new agents and combinations of agents and that determine which treatments are best for prolonging health and life.

Our therapeutic successes against HIV itself have been real, but limited. The oldest drug in our armamentarium, zidovudine, may be best at preventing transmission of the virus from mother to infant, where it can reduce that rate by two-thirds. The administration of zidovudine during early HIV disease does not appear to confer a survival benefit. However, zidovudine does offer such a benefit for patients with full-blown disease, and dideoxyinosine (ddI) has been shown to delay progression. There is as yet little definitive information on the effects of the other nucleoside analogue reverse transcriptase inhibitors on progression or survival. The development of these nucleoside analogues does demonstrate that it is feasible to reduce viral replication, and induce short-term immunologic and clinical benefit. Therefore, the task before us in the coming years is to deepen the magnitude of viral suppression, improve immunological and clinical benefit, and prolong the still tragically limited clinical efficacy of these first-generation antiretroviral agents.

People with HIV infection are living longer now than they did a decade ago. Indeed, the survival time of people with AIDS has doubled, largely due to advances in the treatment and prevention of opportunistic infections. These have been among our greatest successes in AIDS research thus far, and they have provided tangible benefits for people living with the disease.

Pathogenesis-driven clinical trials can teach us a great deal about the virological and immunological aspects of HIV disease *in vivo* by answering basic scientific questions within the framework of a clinical study. We will continue to provide strong support for these pioneering efforts. Similarly, studies of immune-based therapies may provide both new therapeutic approaches to HIV disease and clues to elucidating its pathogenesis.

The NIH AIDS clinical research infrastructure is composed of many networks that grew rapidly and independently of each other in the context of a public health emergency but in the absence of a broad plan for clinical research. They now receive a considerable fraction of the total NIH AIDS research budget. A more complete, coherent, and cost-effective clinical research effort is necessary and possible. With better coordination, these various networks can provide the means for adequately testing new and existing agents and, at the same time, make resources available to other areas.

Drug Discovery

In the area of drug discovery, our efforts to intercede in the viral life cycle have focused primarily on agents directed against the HIV reverse transcriptase and, more recently, the HIV protease. Four reverse transcriptase inhibitors are currently approved by the U.S. Food and Drug Administration for the treatment of HIV infection. Several HIV protease inhibitors are slated to begin Phase III efficacy trials in the near future.

We will place special emphasis on and devote resources to the development of therapies based on new molecular targets in order to broaden our arsenal of weapons against the virus. The recent solution of the three-dimensional structure of the integrase of HIV-1 marks an important step toward the development of agents that may inhibit this critical viral enzyme, potentially providing an additional class of antiretroviral agents. The development of additional classes of drugs will require a more detailed understanding of HIV regulatory proteins, including *tat*, *nef*, and *rev*, and of the less well-studied accessory proteins as well as the design of biologically relevant screens for inhibitors of these gene products.

AIDS researchers have reached a consensus that our drug discovery efforts cannot be limited to antiretroviral agents alone. The pathogenesis of HIV infection is a multifactorial process that involves both direct viral cytotoxicity and indirect effects mediated through the immune system itself. We will intensify our efforts to develop new agents or modalities to intercede in the immunopathogenesis of the disease as well as to find new ways to attack the virus directly.

Currently, several cytokine and anticytokine therapies are being tested for their potential value in HIV infection; among them are interleukin 2, interleukin 12, and the tumor necrosis factor inhibitors, pentoxifylline and thalidomide. Clinical investigators are expanding HIV-specific cytotoxic T lymphocytes for reinfusion into the infected donor of these cells. Others are examining the usefulness of highly targeted immunomodulatory agents to stem those aspects of immune activation that contribute to the progress of the disease. There is also great enthusiasm about the potential of gene therapy for limiting the capacity of cells to support the growth of the virus. We are committed to supporting the development of novel approaches based on our latest understanding of the pathogenesis of the disease and not limiting ourselves strictly to antiviral approaches.

While we have had important successes against opportunistic pathogens, other infections and cancers present us with new challenges, including, for example, cryptosporidium and microsporidium, Kaposi's sarcoma, non-Hodgkin's lymphoma, and progressive multifocal leukoencephalopathy. Furthermore, in this era of increasing antibiotic resistance, many common microbes once thought vanquished are returning with a vengeance. The appearance of multidrug-resistant tuberculosis raises the specter that the monster we thought was slain was merely asleep. Therefore, NIH will intensify efforts to discover and develop new anti-infectives and novel antineoplastic agents.

Vaccine Research

Our greatest hope for the eradication of HIV lies in the development of effective preventive vaccines. Indeed, in many parts of the world, vaccines are the only realistic way to deal with the epidemic. Phase III field trials of two gp120-based vaccines are now planned to be carried out under WHO auspices outside the United States. These vaccine candidates were also considered for such testing within the United States. An NIH advisory committee judged that U.S. trials were not yet warranted because of the concern about the ability of these vaccines to stimulate production of antibody capable of neutralizing primary viral isolates and to generate broadly cross-reactive cytotoxic T-cell responses. These alternative decisions are, in part, a reflection of differences in the nature of the epidemic in different parts of the world and of the potential value of partially effective vaccines in these different settings. The possibility that the available gp120-based vaccines may have only partial or limited effectiveness has forced us to recognize the urgency of the development of second-generation HIV preventive vaccines with enhanced immunogenicity. We must base this effort on the latest knowledge about the virus and the immune response it evokes. Large-scale testing of vaccines will proceed in the United States when reliable scientific evidence suggests that our new candidates have a reasonable degree of promise.

NIH will increase support for studies of the mechanisms of immunological resistance to infection with HIV and related lentiviruses. Work is now proceeding on several unique cohorts of individuals that may hold important clues in this regard. In the Nairobi Sex Workers Study, a group of women who, despite repeated apparent exposure to HIV, have resisted infection are being carefully analyzed. Studies are under way of health care workers who, despite exposure to the virus, have remained uninfected but do show evidence of immune response to viral antigens. These exposed, but uninfected individuals, may have acquired a form of protective immunity; understanding the nature of this immunity can provide insight into what is required for effective vaccine-based prevention.

Animal models, particularly the SIV-infected macaque, will be important in understanding the details of pathogenesis and in establishing the nature of protective immunity. It is particularly important to understand the nature of the immunity to a fully virulent SIV that is induced by vaccination with a *nef*-deleted viral mutant. NIH is supporting studies of these immune responses and will take an active role in determining whether attenuated viruses can be developed that are sufficiently safe to warrant serious consideration as vaccine candidates. Risk/benefit ratios of an attenuated virus vaccine will vary depending on infection rates and other considerations. An attenuated virus vaccine may be entirely appropriate in certain regions but less appropriate in others.

An immune response that slows progression of an established infection may be very different from one that protects against initial infection with the virus. Long-term nonprogressors, those individuals who remain immunologically intact more than a decade after seroconversion, may share unique immune responses that are particularly potent against the virus once infection has been established. The analysis of these responses promises to provide important clues for us in the effort to understand the characteristics of an immune response that is effective in HIV-positive individuals.

Behavioral Research

Currently, behavioral interventions are our only weapon against the spread of the epidemic. Behavioral research is a large and vital part of the NIH AIDS research portfolio. One of our challenges will be to better integrate our biomedical and behavioral research programs. Behavioral components of both vaccine and drug clinical trials will be essential to obtaining reliable results.

The Institute of Medicine (IOM) of the U.S. National Academy of Sciences recently released a report on the state of research in this area. Several key recommendations in the IOM report will be carefully considered as we map the future of behavioral research on AIDS. Among them is to obtain reliable information on sexual practices and substance abuse in order to more clearly elucidate HIV risk-taking behavior. Investment in behavioral research should provide us with better intervention strategies to prevent HIV transmission. We must also build the base of fundamental behavior research in order to develop effective and durable strategies through which risk-taking behavior can be controlled.

Other prevention strategies, particularly virucides and female-controlled barriers of HIV and STD infection, are critically needed to give women additional options with which to protect themselves. The NIH has initiated a major program to develop such barriers and in the coming year will substantially increase the funds devoted to this effort.

In summary, the NIH AIDS research budget request is framed on the following scientific priorities:

- A rededication to fundamental science;
- A vigorous therapeutic research program, emphasizing both drug discovery and an efficient clinical trials system, with additional emphasis on increased participation of women, minorities, and other underrepresented populations;
- A stronger effort to develop second-generation vaccines and to bring them to clinical trial as soon as possible; and
- An emphasis on prevention, including enhanced studies of risk-taking behavior and the development of strategies to avert infection, such as female-controlled barriers and STD treatment and prevention.

These exciting opportunities hold great promise for advancing our knowledge toward the development of more useful therapeutics, effective vaccines, and practical prevention strategies. The specific objectives from the *FY 1996 NIH Plan for HIV-Related Research* are those that the OAR has judged to have the greatest likelihood of attaining the goals that have been set forth and of making tangible progress against AIDS.

The following is a listing of the FY 1996 Areas of Emphasis with the objectives:

National History and Epidemiology

Objective 1:	Develop and assess intervention strategies to reduce or prevent HIV transmission
Objective 2:	Characterize the risk factors and mechanisms of HIV transmission in various populations
Objective 3:	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease
Objective 4:	Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease
Objective 5:	Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing

Etiology and Pathogenesis

Objective 1:	Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction
Objective 2:	Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression

Objective 3: Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies

Objective 4: Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases

Objective 5: Elucidate the pathogenesis of HIV-related opportunistic infections

Objective 6: Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation

Objective 7: Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases

Therapeutics

Objective 1: Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry

Objective 2: Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies

Objective 3: Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals

Objective 4: Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users

Objective 5:	Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child
Objective 6:	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis
Objective 7:	Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection
Objective 8:	Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications

Vaccines

Objective 1:	Increase scientific knowledge about host defense mechanisms and protection against HIV infection and disease
Objective 2:	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models.
Objective 3:	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials
Objective 4:	Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population
Objective 5:	Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials

Objective 6:	Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met

Behavioral Research

Objective 1:	Prevent new HIV infections through behavior interventions. Translate findings from behavioral and social science research to design, implement, and evaluate interventions in diverse settings and populations
Objective 2:	Strengthen the behavioral science base. Conduct a wide range of studies to expand knowledge of the principles of behavior and behavior change
Objective 3:	Preventing the negative consequences of HIV infection. Discover, develop, and evaluate strategies to prevent or minimize the physical, psychological, cognitive, and social consequences of HIV, including strategies to improve adherence to proven therapies and recruitment, retention, and adherence to clinical trial protocols
Objective 4:	Create and test innovative dissemination strategies. Develop, assess, and rapidly disseminate research findings and treatment strategies to give researchers and communities access to state-of-the-art communications
Objective 5:	Strengthen the behavioral and social science infrastructure. Develop multidisciplinary and interagency collaborative efforts to enhance the AIDS behavioral research effort; enhance the behavioral aspect of research into therapeutics, natural history and epidemiology, and vaccines. Train researchers to conduct basic and applied social science research related to HIV. Provide the state-of-the-art physical facilities and equipment that are necessary to conduct HIV-related behavioral and social science research within relevant settings

Training and Infrastructure

Objective 1:	Provide both domestic and international training in biomedical and behavioral research on HIV

Objective 2: Establish appropriate infrastructure for the conduct of HIV research domestically and internationally

Information Dissemination

Objective 1: Expedite the dissemination of the latest information on clinical trials, state-of-the-art therapies, health care, and prevention techniques to domestic as well as international audiences as appropriate

TUESDAY, MARCH 14, 1995.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. ANTHONY S. FAUCI, DIRECTOR

MICHAEL I. GOLDRICH, DEPUTY DIRECTOR FOR MANAGEMENT AND OPERATIONS

DR. GEORGE COUNTS, DIRECTOR, OFFICE OF RESEARCH ON MINORITY AND WOMEN'S HEALTH

DR. JOHN J. McGOWAN, DIRECTOR, DIVISION OF EXTRAMURAL ACTIVITIES

STEVEN J. BERKOWITZ, FINANCIAL MANAGEMENT OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. Dr. Fauci, I am delighted to see you. Dr. Varmus said you could cure my cold.

I really regret having to miss half of the hearing with Dr. Varmus this morning because I had to go first to the Rules Committee and then to a press briefing on the rescission package with the Chairman of the full Committee. I don't have any similar constraints this afternoon, so we are delighted to have you here.

We look forward to hearing your testimony, and if you would begin by introducing your colleagues at the table and then proceed.

INTRODUCTION OF WITNESSES

Dr. FAUCI. Thank you very much, Mr. Chairman.

On my immediate left at the end of the table is Dr. George Counts, the Director of our Office of Research on Minority and Women's Health; next to him is Dr. John McGowan, Director of the Division of Extramural Activities; this is Mr. Michael Goldrich, my Deputy Director for Management and Operations; this is Mr. Steven Berkowitz, our Financial Management Officer, and you know Dr. Varmus and Mr. Williams.

OPENING STATEMENT

I have submitted my written statement for the record, Mr. Chairman, and with your permission I would like to give a brief opening oral statement with the help of some posters here.

Mr. Chairman, as you know, over the last several years when I have come before this committee we have stressed the National Institute of Allergy and Infectious Disease's complement to fundamental basic research in microbiology and infectious diseases, which immediately has some important practical applications to the public health as we will get into, I am sure, in the discussions of the hearing.

I would like to underscore and reemphasize the importance of fundamental basic research, which we look upon as a laboratory-to-bedside, bedside-to-laboratory approach. We take problems that we see at the laboratory to the bedside, bring them back to the laboratory and in the most sophisticated way technology allows, ask questions, answer them, and try to get back to applying the answers to a variety of infectious diseases.

Immunologically mediated diseases also lead to advances in therapies not only for infectious and immunological diseases but for a number of crossover diseases, and for vaccines and diagnostics. Of course, if we had not had the fundamental underpinnings of basic research in microbiology and immunology, we would never have been able to hit the ground running with AIDS research as we did several years ago.

Let me give you one cogent example of that, and that is research which has really revolutionized the way we can diagnose disease, that being polymerase chain reaction, or PCR, which many of us are familiar with now from the forensic medicine applications we see every day with the O.J. Simpson trial.

But, in fact, PCR is used as a diagnostic test in a number of important diseases. It was basic research on a somewhat obscure microorganism, called *Thermus acquaticus,* which resulted in the PCR assay. *Thermus acquaticus* has the interesting characteristic of being able to survive in very hot temperatures, actually in hot springs. It is an enzyme from *Thermus acquaticus* which allows the function of PCR at very high temperatures.

What this has allowed, as I mentioned, is a diagnostic test for a disease that has assumed great importance in the United States today, and that is Lyme disease, the most important vector-borne disease in the United States today. We have discussed this before in this committee many times in the past. PCR is also used to diagnose HIV and a variety of other infectious diseases.

Another example of the practical application of fundamental basic research to the health of patients is something Dr. Varmus mentioned to you this morning. That is the use of interleukin-2, a protein, or cytokine as we call it, that is made by immune competent cells and is an important product for the normal homeostatic regulation of the immune response, which makes all our immune systems work normally.

First, patients with HIV infection have a defect in IL–2 secretion, especially when their lymphocyte counts drop below a certain level, which puts them in grave danger for opportunistic infections. There are several ways to try to get around that, and one of them is to directly attack the virus the way several of the antiretrovirals do, including the protease inhibitors you heard about this morning.

However, returning the immune system to a normal level is a very problematic thing. An NIH study recently reported in the New England Journal of Medicine, showed that the use of this particular protein, IL–21, together with antivirals which actually caused a rather dramatic increase in the lymphocyte counts of individuals, putting them well within the normal range.

If, together with antivirals, we can use this protein, given intermittently every eight weeks or even longer than every eight weeks, we may be able to keep the lymphocyte counts within the normal range. If so, I think we are another step further towards moving HIV-infected individuals from the grave danger of being subject to diseases such as those caused by opportunistic infections.

What about the economic impact? Again, a question that was asked of Dr. Varmus this morning.

From our Institute, a couple of examples of investments made in research and translated into potential annual savings, are antiviral therapy for neonatal herpes, in which $5 million was invested by the Institute with a return annually of over $180 million; AZT, to prevent perinatal transmission of HIV from an infected mother to an infant, an $8 million investment that has translated into a potential savings of $170 million; treatment to prevent kidney rejection, $1.7 million cost to a potential $40 million savings. An important success story for environmental research is a collaboration between NIAID and the Child Health Institute in which we invested about $20 million in a vaccine *Haemophilus influenzae b,* which is now being translated into a potential annual savings of $400 million or more. And I will tell you a little more about that.

Haemophilus influenzae b is the most important cause of childhood deafness and mental retardation. Within the first few months of life, children can develop meningitis which leads to devastating neurological consequences. The incidence of infection per 100,000 children aged 6–12 months was 135 prior to a truly effective vaccine.

The vaccine we had was one to which infants did not respond very well. When a conjugate vaccine was licensed for individuals who were 18 months old, we started to see a decrease in the incidence of this disease. Now, with the conjugate vaccine licensed for individuals less than two months old, we are seeing a phenomenon, again something Dr. Varmus alluded to this morning, where we actually have the potential of eliminating a devastating disease.

And that is right where we are right now with *Haemophilus influenzae b*. By immunizing these children at a very early age we are seeing the virtually complete disappearance of the most important cause of mental retardation and deafness in children.

Mr. HOYER. Are those national figures?

Dr. FAUCI. Those are national figures, Mr. Hoyer. Just as you can get rid of diseases, there are diseases that continue to emerge and reemerge.

[CLERK'S NOTE.—Subsequent to the hearing, NIAID indicated the data are from Los Angeles county.]

We heard talk this morning about Richard Preston's book Hot Zone, as well as the movie that was released this weekend called Outbreak. That is not necessarily so much science fantasy here. We now know, of diseases that we never heard of before, like HIV or diseases that have reemerged in this country, like tuberculosis or Hantaan virus, which we originally had experience with in the Korean war, then known as Korean hemorrhagic fever, which has now reemerged in the southwestern part of the United States.

We also know about the group A streptococcus which is called, inappropriately, the flesh eating bacteria, as well as *E. coli* that causes food poisoning in children. These are organisms that we must constantly guard against since these and other microbes might emerge or reemerge in our country. The AIDS experience tells us this is not just a fantasy, but can, in fact, occur.

The NIH's response to that is fundamental research. When you are talking about infectious diseases, it's research in microbiology and immunology. In the movie—I don't know if any of you saw it—they decided they would nuke a village because people were infected. We prefer not to do any nuking of villages, but to nuke the microorganism, which is what basic research is about.

Finally, let me just close with a little more detail on the answer to the question Ms. Pelosi asked of Dr. Varmus this morning, about the applications of AIDS research. We see that the investment made in AIDS research has already, led to advancements in diseases that transcend AIDS. We can point to them and will point to them more in the future.

These include diagnostics of all types, antivirals, improvements in the treatment of immunological diseases, better understanding of the immune system, organ transplantations, advances in molecular biology and the neurosciences, as well as in the treatment of opportunistic infections in people who have cancers get because of the treatment we give them.

So, you see, it takes us full cycle. We started with basic research applied to diseases such as AIDS. We are seeing the positive spin-offs now for a specific disease, HIV/AIDS, which is having positive spin-offs now, and in the future for other diseases.

That is my opening statement. I would be happy to answer any questions, Mr. Chairman.

[The prepared statement and biography of Dr. Anthony Fauci follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Allergy and Infectious Diseases

For more than four decades, the National Institute of Allergy and Infectious Diseases (NIAID) has developed increasingly better means of preventing, diagnosing, and treating allergic, immunologic, and infectious diseases. During the past year, a number of important advances, with extraordinary implications in both human and economic terms, were reported. Hence, the American people continued to benefit from the sustained investment by NIAID in basic and clinical research.

One of the most exciting developments during the past year occurred in our battle to protect children from HIV infection. NIAID-supported investigators found that the drug AZT can reduce by two-thirds the rate of HIV transmission from mother to infant when given to women during the last 20 weeks of pregnancy and during labor and delivery, and to their infants during the first six weeks of life. The use of AZT in HIV-infected pregnant women could potentially prevent the infection of 1200 infants each year in this country. In addition to sparing these babies from the devastating consequences of HIV disease, the annual savings to the U.S. health care system could be as much as $170 million in direct medical care costs.

NIAID-supported researchers also have made important progress against chlamydia, the most common sexually transmitted bacterial pathogen in the United States. They have developed a highly sensitive urine test for detecting chlamydial infections, even in people who have no symptoms. Extensive use of the assay would allow early treatment of many asymptomatic individuals, thereby preventing the adverse consequences of the disease, especially pelvic inflammatory disease and infertility in women. Such treatment could reduce the $2.7 billion in annual direct and indirect costs associated with chlamydial infections in the United States.

Development of new and improved vaccines is a priority for NIAID. Vaccines provide safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases. The eradication of smallpox was possible because a simple, effective, and inexpensive vaccine was available. Similarly, with the elimination of polio from the Americas, global eradication of this infection is now a realistic goal.

In addition to vastly improving the public's health and well-being, vaccines can markedly decrease both direct and indirect health care costs. For example, it has been calculated that at least $14 (direct and indirect costs) is saved for every dollar spent on measles, mumps, and rubella immunization in this country. Considering that infectious diseases account for 25 percent of all visits to physicians each year, at a total annual cost to society that may exceed $120 billion, the importance of research into disease prevention by vaccination cannot be overstated.

Widespread use of vaccines that employ technology developed by NIAID-supported researchers has virtually eliminated disease caused by *Haemophilus influenzae* type b (Hib) in this country, saving $400 million each year in direct and indirect costs. Prior to the availability of an effective Hib vaccine, Hib meningitis, a leading cause of hearing loss and mental retardation in pediatric patients, afflicted 10,000 to 15,000 children annually.

Another vaccine based on the work of NIAID researchers appears to be safe and effective in the prevention of disease caused by hepatitis A virus. This food- and water-borne disease affects more than 130,000 individuals each year in the United States. Protection of persons at high risk for hepatitis A infection, such as travelers to countries where the disease is endemic, promises substantial reduction of the $300 million in direct and indirect costs associated with hepatitis A annually in the United States.

NIAID researchers also have provided the first firm evidence that a vaccine used as a therapy can modify the course of a chronic viral infection. Intramural scientists and their collaborators found that an experimental herpes vaccine safely reduced by one-third the number of outbreaks of genital herpes in people with frequent recurrences of the disease. Further development of this vaccine may help the 10 million Americans who have recurring genital herpes infections, and reduce the direct and indirect costs of herpes infections, estimated to be $102 million annually.

Through 1994, more than 440,000 individuals in the United States had been diagnosed with AIDS; another 560,000 may be HIV-infected but have not yet developed AIDS-related symptoms. HIV infection is now the leading cause of death among adults aged 25 to 44 in the United States. It has been estimated that the lifetime cost of treating an individual with HIV infection is $119,000.

The human and economic toll of the disease is an important impetus to our efforts to develop an effective vaccine against HIV. There are a number of promising vaccines in the pipeline at various stages of development, and the Institute is organizing the resources and personnel to facilitate large-scale vaccine testing as soon as candidate vaccines are identified.

To help those already infected with HIV, the Institute is stimulating innovative approaches to therapies to fight HIV and HIV-associated infections, with the goal of prolonging and improving the quality of life. Toward this end, the Institute has initiated the Strategic Program for Innovative Research on AIDS Treatment to explore cutting-edge strategies using gene therapy and immune system restoration, and to move these novel concepts from the laboratory into pilot clinical studies.

Five NIAID-supported gene therapy trials for HIV disease have been approved or are awaiting approval by the U.S. Food and Drug

Administration. One of these studies, for example, involves removing immune system cells from HIV-infected patients, inserting a gene into these cells, and returning them to the patients. The gene produces an enzyme that cuts the genetic material of HIV, preventing it from replicating.

Another experimental HIV therapy involves the administration of immune system molecules called cytokines. NIAID intramural investigators have found that infusions of the cytokine interleukin-2 can significantly increase the crucial immune system cells that are depleted in HIV infection. Ongoing clinical trials at the NIAID are determining the clinical significance of these findings.

Intramural research at the NIAID has also revealed important clues about why a small minority of HIV-infected people have remained healthy without loss of immune function for 10 or more years. Levels of HIV and viral replication are far lower in these individuals, termed "long-term non-progressors," than in those whose disease progression is more typical. In addition, the internal structure of the non-progressors' lymph nodes, unlike those of most people with HIV infection, appears essentially undamaged. Further studies of long-term non-progressors will determine the mechanisms that prevent the onset of advanced HIV disease and AIDS. Such studies may provide important insights relevant to the development of new vaccines and treatments for HIV infection.

Our AIDS research effort promises to benefit not only those infected with HIV, but also individuals with other infectious diseases, immunologic diseases, and cancer. AIDS research has provided, for example, new insights into the interactions between microbes and the immune system, new strategies for drug and vaccine development, and a better understanding of basic cellular processes.

Another important threat to the Nation's health is Lyme disease, the most common tick-borne infection in the United States. The Institute continues a substantial effort toward understanding, treating, and preventing this disease. Two large-scale tests of Lyme disease vaccines based on NIAID-supported research on a protein found on the surface of the Lyme bacterium are now underway. Previous studies of these vaccines in a small number of individuals showed that they are safe and can evoke protective immune responses.

A critical issue in the study of Lyme disease is whether chronic Lyme disease, which is characterized by symptoms that persist after antibiotic treatment, is related to an ongoing infection, an adverse immune response that continues after the organism has been eradicated and injures host tissues, or other factors. We are working to design a pilot study to help answer these questions.

NIAID's research holds special promise for helping women, who bear a disproportionate burden of conditions such as autoimmune diseases and chronic fatigue syndrome, and members of minority groups, who suffer from conditions such as asthma and need organ transplants more often than whites.

Autoimmune diseases such as multiple sclerosis (MS) occur in 5 percent of adults in the United States, two-thirds of them female. MS is the most common progressive neurologic disease of young Americans, affecting an estimated 250,000 to 350,000 persons in the United States. In the past year, NIAID researchers have reported a promising new approach to therapy: repeated intravenous injections of the nerve cell protein attacked by immune cells in people with MS. This treatment triggers the suicide of the specific cells that attack the nerves. In a mouse model of MS, the effect of the treatment has been striking -- untreated mice were barely able to move around their cages but treated mice improved remarkably. The researchers are currently designing a clinical trial to evaluate the treatment in human patients.

The Institute is committed to unraveling the complex problem of chronic fatigue syndrome, a very real disease that has profoundly affected the lives of many Americans. Working in conjunction with an international group of CFS experts and constituency groups, NIAID played a key role in a recent report that provides a new conceptual framework to guide the development of research questions, a revised case definition, and clinical guidelines for evaluating patients with CFS. As a result, research results should be easier to compare, and the cause or causes of the illness and ways to treat or prevent it may be easier to find.

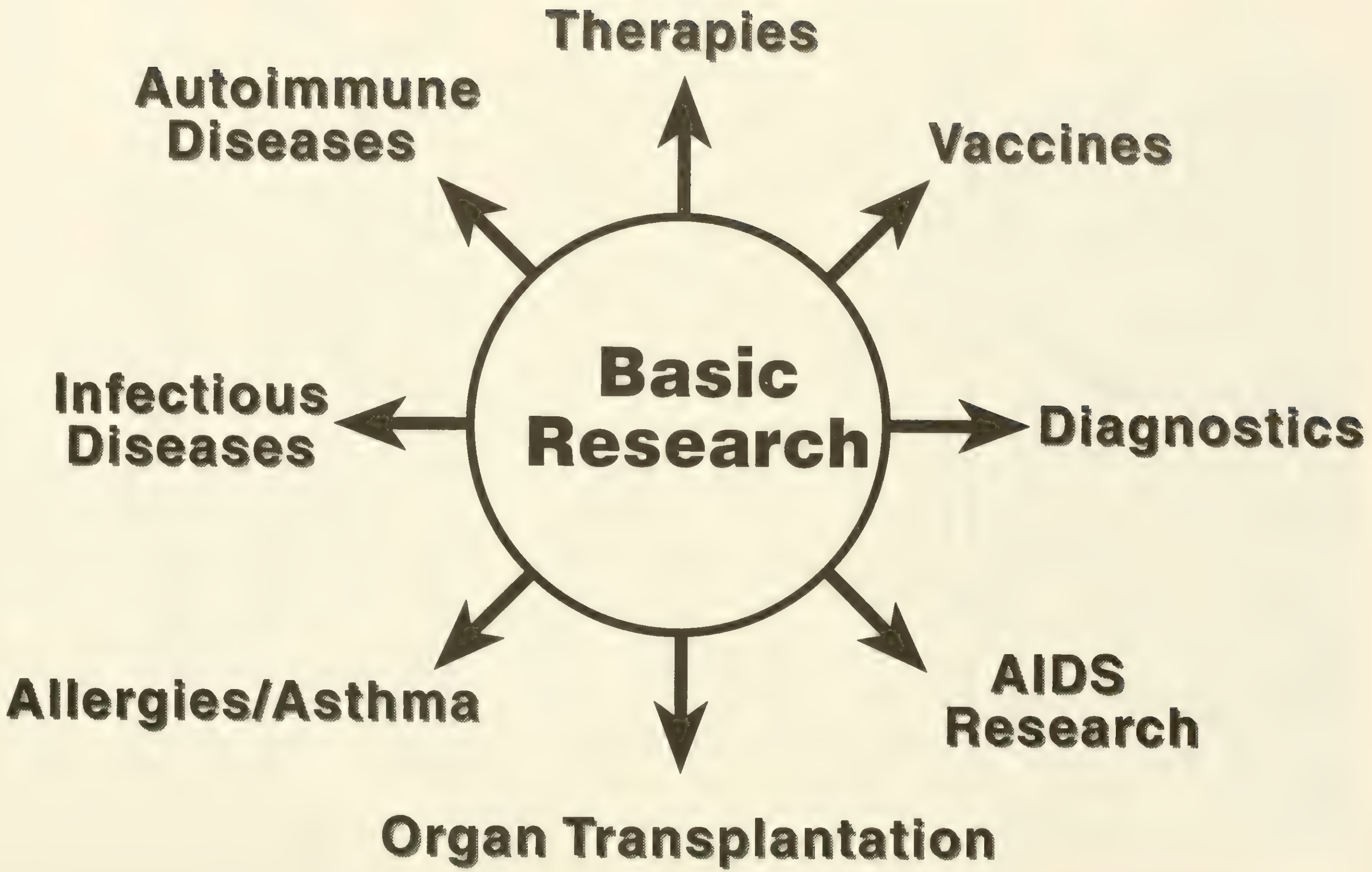
Asthma costs the country an estimated $7.4 billion annually in direct and indirect expenditures. As I have discussed in previous years, asthma rates have been rising, especially among minority children in our cities. Despite the availability of effective therapies for the disease, mortality rates increased 6.2 percent per year during the 1980s among 5- to 34- year olds, with the greatest increases among non-whites. Because of the urgency of this problem, scientists in NIAID's National Cooperative Inner-City Asthma Study, which has sites in eight cities, are evaluating the factors involved in the rise of asthma and designing intervention strategies. Last August, the Institute launched an asthma intervention trial enrolling 1,000 inner-city children to identify ways to reduce severe asthma episodes and deaths among high-risk groups.

Minorities also bear a disproportionate burden of certain diseases that result in the need for transplanted organs. Transplants have saved the lives of thousands of patients and provided an extraordinary improvement in the quality of life for tens of thousands of others. NIAID is working to improve and increase the availability of tissue typing reagents and to develop ways to improve transplant tolerance. In the past year, NIAID-supported research in transplantation identified new transplantation antigens in African-Americans that will allow better tissue matching and greater access to transplants. As this effort continues, we anticipate that our ability to tissue-type African-Americans will greatly improve.

Despite the advances I have outlined, the health of all Americans remains vulnerable to new threats. The spectrum of infectious diseases continues to evolve: we have seen the emergence of newly identified pathogens and syndromes including HIV, Legionnaire's disease, Lyme disease, toxic shock syndrome, hepatitis C and, most recently, the hantavirus pulmonary syndrome caused by rodent-borne viruses. Life-threatening illnesses due to a virulent, food-borne strain of the bacterium *E. coli* have occurred in several states, and a rise in cases of necrotizing fasciitis due to invasive group A streptococcal infection has been documented. In addition, our Nation faces the specter of drug-resistant strains of a number of pathogens, including those that cause tuberculosis and pneumococcal pneumonia.

These current threats to our health, and the certainty that new challenges will emerge, underscore the importance of continued support of basic biomedical research in immunology and infectious diseases, which historically has led to new and improved vaccines, diagnostic tools, and treatments. Using the modern tools of molecular biology, NIAID continues to build the research foundation that will lead to further advances in protecting the health of future generations.

Mr. Chairman, the FY 1996 budget request for this Institute is $557,354,000. I will be pleased to answer any questions you may have.


Therapies
Autoimmune Diseases
Vaccines
Basic Research
Infectious Diseases
Diagnostics
Allergies/Asthma
AIDS Research
Organ Transplantation

Basic Research on T. Aquaticus Led to Diagnostic Tool for Lyme Disease

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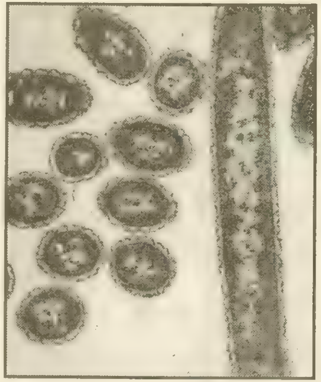
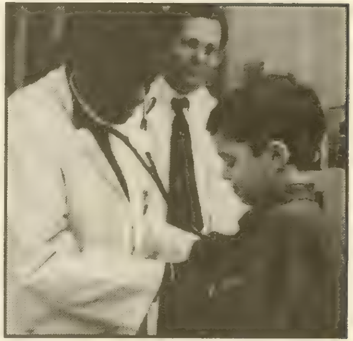


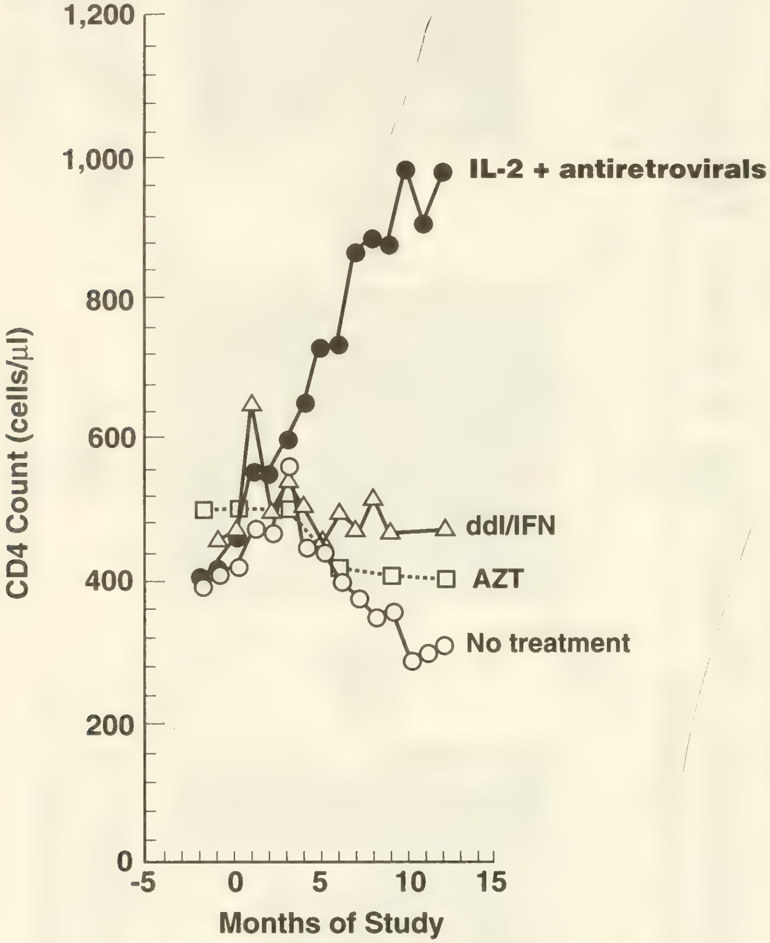
Basic Research

PCR

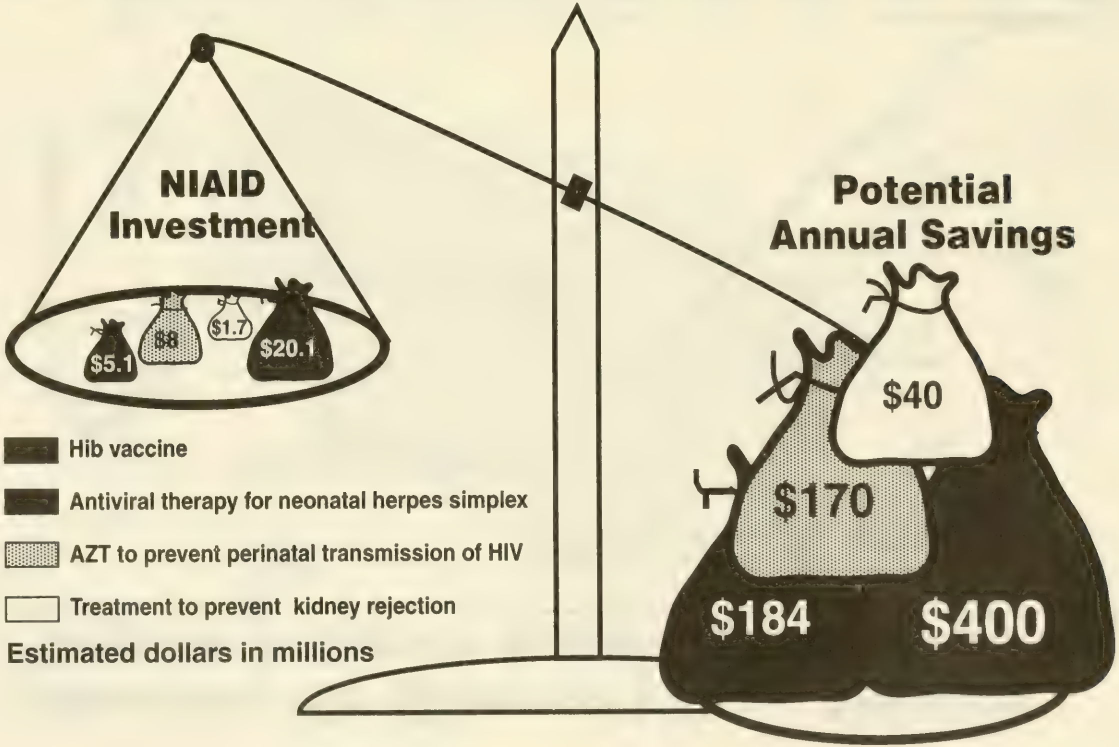


Diagnostic Tool for Lyme Disease

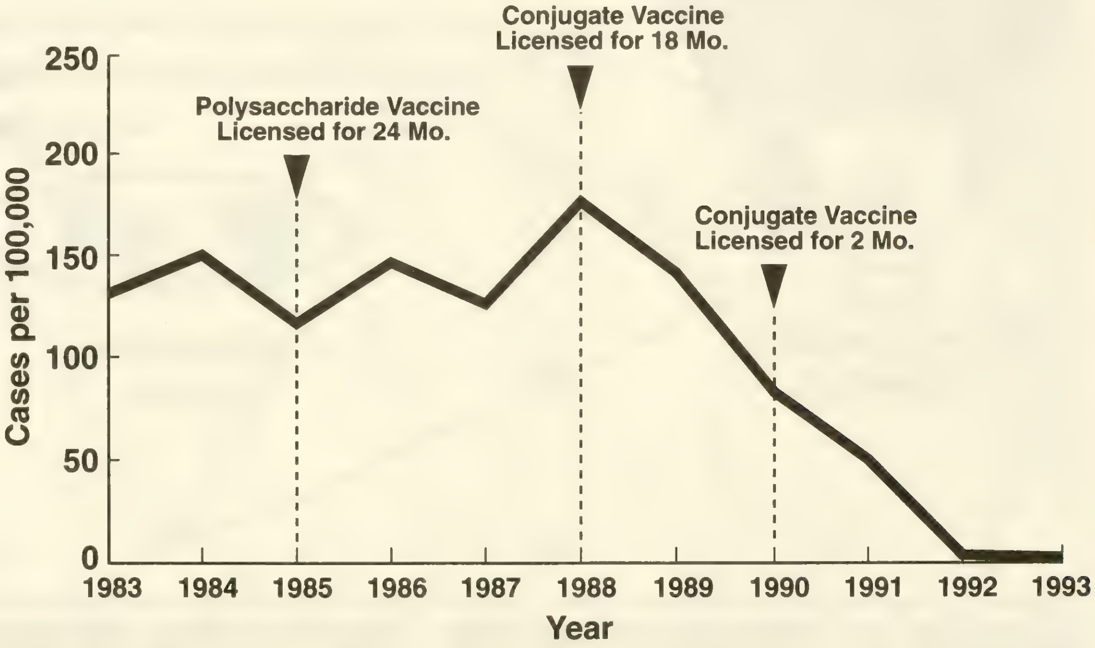
Changes in CD4 Counts in HIV-Infected Individuals Receiving Intermittent, Continuous Infusion Interleukin-2



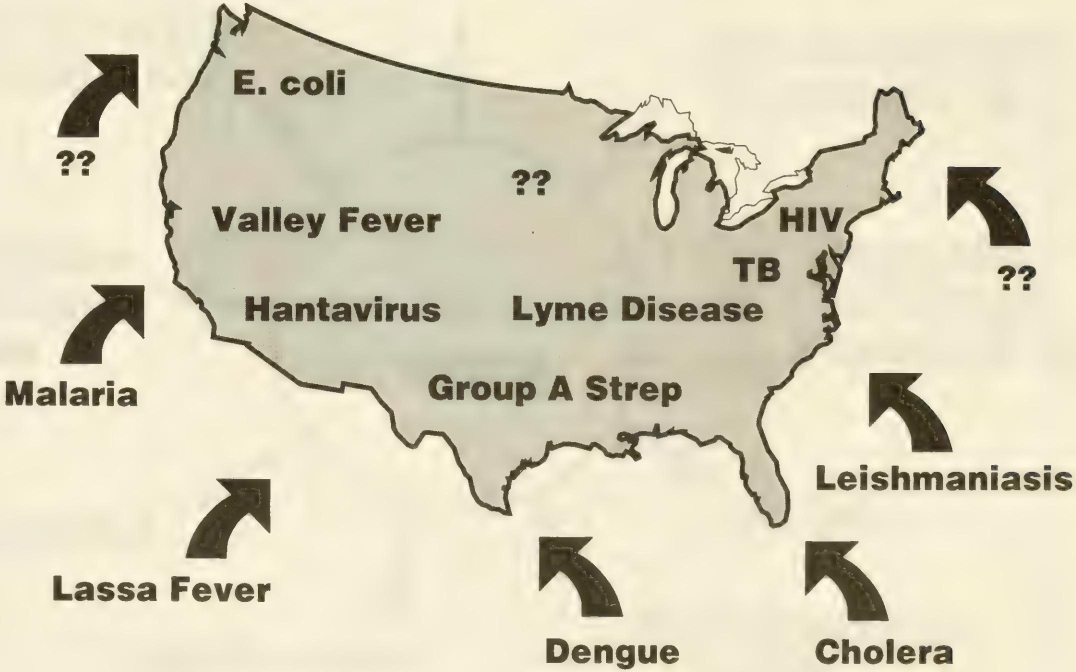
NIAID Research: An Investment in Health

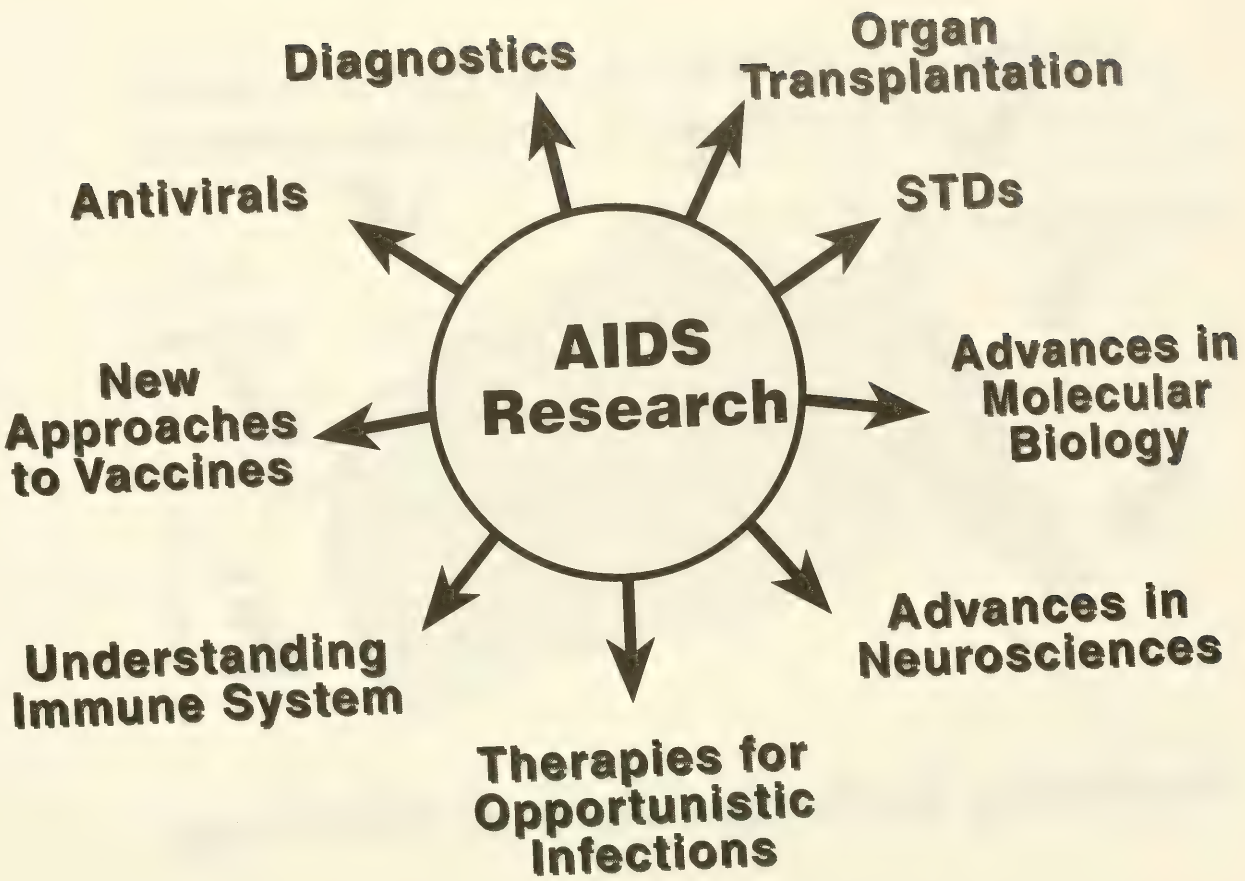


Invasive Hib Disease in Los Angeles County Children Aged 6-12 Months



Emerging and Re-emerging Diseases




Diagnostics
Organ Transplantation
Antivirals
STDs
AIDS Research
New Approaches to Vaccines
Advances in Molecular Biology
Understanding Immune System
Advances in Neurosciences
Therapies for Opportunistic Infections

FAUCI, DR. ANTHONY S.
Director, National Institute of Allergy and Infectious Diseases

December 24, 1940. Brooklyn, New York

Education:

College of Holy Cross, 1962 - A.B.; Cornell University Medical College, 1966 - M.D.

Professional History:

1966-1967, Intern, Department of Medicine, New York Hospital-Cornell Medical Center. 1967-1968, Assistant Resident, Department of Medicine, The New York Hospital-Cornell Medical Center. 1968-1970, Clinical Associate, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. 1970-1971, Senior Staff Fellow, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1971-1972, Chief Resident, Department of Medicine, New York Hospital-Cornell Medical Center; Instructor in Medicine, Cornell Medical College. 1972-1974, Senior Investigator, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1972-present, Consultant in Infectious Diseases, The National Naval Medical Center, Bethesda, Maryland. 1974-1980, Head, Clinical Physiology Section, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1977-1984, Deputy Clinical Director, NIAID, NIH, Bethesda, Maryland. 1980-present, Chief, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland. 1984-1988, Clinical Professor, Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine, Washington, D.C. 1985-1988, Clinical Professor, George Washington University School of Medicine and Health Sciences, Washington, D.C. 1988-1994, Director, Office of AIDS Research, NIH, and Associate Director of NIH for AIDS Research, Bethesda, Maryland. 1984-present, Director, NIAID, NIH, Bethesda, Maryland.

Board Certification and Military Service:

American Board of Internal Medicine-June 21, 1972. American Board of Allergy and Immunology-March 1, 1974. American Board of Infectious Diseases-October 15, 1974. U.S. Public Health Service, July 1968-June 1970; July 1972-Present.

Professional Organizations:

American Federation for Clinical Research, American Association for the Advancement of Science, American Association of Immunologists, American Medical Association, Fellow of the American Academy of Allergy, Infectious Diseases Society of America, American Society for Clinical Investigation, Fellow of The American College of Physicians, Member, Association of American Physicians, Fellow of the Collegium Internationale

Allergologicum, Charter Member of the Clinical Immunology Society, International AIDS Society, American Society for Virology, Fellow of the American Academy of Arts and Sciences, Member of the Institute of Medicine of the National Academy of Sciences (USA), Foreign Member of the Royal Danish Academy of Sciences and Letters, Member of the National Academy of Sciences (USA).

Offices Held:

Councillor, Eastern Section, American Federation for Clinical Research (AFCR), 1977. National Councillor, AFCR, 1978-1979. President, AFCR, 1980-1981. Recorder, Association of American Physicians, 1988-1993. Councillor, Association of American Physicians, 1993-present.

Advisory Boards and Committees:

Chairman, Allergy and Immunology Committee, MKSAP V, American College of Physicians. Advisory Panel, The American Board of Medical Laboratory Immunology. Member, Committee on Clinical Immunology and Immunopathology, American Association of Immunologists, 1980-1985. Representative of American Association of Immunologists to the Examinations Committee of the American Board of Allergy and Immunology, 1981-present. Postgraduate Education Committee, American Academy of Allergy, 1979-1982. Member, NIAID Study Group on Immunology, 1980. Member, Section of Physiology in Clinical Science of the American Physiological Society, 1980-1984. Member, Subcommittee on the Classification of Vasculitis, American Rheumatism Association 1980-present. Ad Hoc Committee, The National Foundation for Infectious Diseases, 1980-present. Subcommittee on Clinical Sciences, Publications Committee, American Physiological Society, 1980-1984. American Association of Immunologists, 1982-1985. Member, NIAID Working Group for AIDS, 1982-present. Member, American Federation for Clinical Research President's Public Policy Advisory Committee, 1983-present. Board of Directors, American Board of Allergy and Immunology, 1984-1987. Participant in the USA - People's Republic of China Immunology Cooperative Agreement, August 10-22, 1983, Beijing and Shanghai, PRC. Member, Scientific Advisory Board, Medical Biology Institute, La Jolla, CA, 1983-1984. Participant in the USA-Japan Eye Immunology Advisory Conference, November 27 to December 1, 1983, Honolulu, HI. Member, External Advisory Committee, Multipurpose Arthritis Center, Duke University Medical Center, 1984-present. Member, Honorary Advisory Board, Italian-American Medical Association, 1984-present. Member, Peripatetic Club, 1984-present. Ex Officio Member, National Diabetes Advisory Board, 1984-present. Ex Officio Member, National Digestive Diseases Advisory Board, 1984-present. Chairman, Search Committee for Director, National Institute of Child Health and Human Development, 1985. Member, Department of Health and Human Services Task Force on Alzheimer's Diseases. The Albert Lasker Medical Research Award Jury, 1985-present. Deputy Ethics Counselor, Department of Health and Human

Services, 1985-present. Member, Department of Health and Humans Services Committee to Coordinate Environmental and Related Programs, 1985-present. Member, Scientific Organizing Committee, Joint Meeting of the Italian Society of Immunology and Immunopathology-National Institutes of Health on "Human Lymphocyte Activation," Florence, Italy, September 5-7, 1985. Member, United States Delegation to the United States-Japan Cooperative Medical Science Committee, 1985-present. Member, U.S. Public Health Service AIDS Executive Task Force, 1985-present. Chairman, NIH AIDS Executive Task Force, 1985-present. Coordinator, NIH AIDS Research, 1985-present. Member, Scientific Seminar Subcommittee, National Institutes of Health Centennial Program, 1985-1987. Member, Advisory Board, Clinical Immunology Newsletter, 1986-1988. Member, Scientific Organizing Committee, International Conference on Lymphocyte Activation and Immune Regulation, Newport Beach, CA, February 28-March 2, 1986. Member, Planning Committee, Clinical Immunology Society, 1986. Member, International Advisory Committee, International Conference on AIDS, Paris, France, June 23-25, 1986. Member, Advisory Group, Institut Scientifique Roussel-Uclaf, 1987-1989. Ex Officio Member, National Kidney and Urologic Diseases Advisory Board, 1987-present. Member, International Programme Committee, 8th International Congress of Immunology, Budapest, Hungary, 1987. Member, International Advisory Committee,IVth International Conference on AIDS, Stockholm, Sweden, June 12-16, 1988. Member, NIH Resource Allocation Group, 1987-1989. Member, Committee for the Coordination of Research Programs on the Acquired Immunodeficiency Syndrome of the Ministry of Health of Italy, 1988-present. Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS, January 17, 1989, through December 31, 1993. Member, Selection Committee for the National Public Service Awards, 1990.

Editorial Boards:

Dr. Fauci has been or is on the Editorial Board of 28 scientific journals in the field of immunology, allergy and infectious diseases. These include: The Journal of Clinical Investigation, The Journal of Immunology, Journal of Infectious Diseases, Journal of Clinical Immunology, The Journal of Experimental Medicine, The New England Journal of Medicine. Dr. Fauci is also the Editor of one of the major textbooks of medicine in the world, "Harrison's Principles of Internal Medicine."

Awards and Honors:

Alpha Omega Alpha. Kileen Prize for Excellence in Chemistry (College of the Holy Cross). John Metcalfe Polk Prize for General Efficiency (Cornell University Medical College). Alfred Mortitz Michaelis Prize for Efficiency in General Medicine (Cornell University Medical College). U.S. Public Health Service Meritorious Service Award, 1979. Arthur S. Flemming Award, 1979 - Given to the 10 outstanding employees in the U.S. Federal Government. Squibb Award of the Infectious Diseases

Society of America, 1983. U.S. Public Health Service Distinguished Service Medal, 1984. Food and Drug Administration Commissioner's Special Citation, 1984. 1985 Citation Classics (Current Contents) for article - A.S. Fauci, D.C. Dale, and J.E. Balow: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann. Intern. Med. 84: 304-315, 1976. Who's Who in America, 44th Edition. Who's Who in Science and Technology, 2nd Edition. 1985 Stanford University Center Survey of the American Rheumatism Association membership ranked the work of Dr. Anthony S. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the past 20 years. The Clemens von Pirquet Award of Georgetown University Medical Center, 1986. Doctor of Science, Honoris Causa, College of the Holy Cross, Worcester, MA May 29, 1987. The Kober Lecture Award of the Association of American Physicians, 1988. Public Health Leader of the Year Award of the Commissioned Officers Association of the U.S. Public Health Service, 1988. The National Institutes of Health Clinical Center Annual Distinguished Clinical Educator Award, 1988. 1988 Citation Classics (Current Contents) for article - A. S. Fauci, B. F. Haynes, P. Katz: The spectrum of vasculitis. Ann. Intern. Med. 89: 660-676, 1978. The Leadership Award of the Columbus Citizens Foundation, Inc., for "Inspired Leadership and Outstanding Achievement in the Field of Medical Research," New York, NY October 8, 1988. American Association for the Advancement of Science/Westinghouse Award for Public Understanding of Science and Technology, 1988. The National Hemophilia Foundation Special Award for Research in AIDS, 1989. The Lee P. Brown National Public Service Award of 1989 presented by the National Academy of Public Administration and the National Society for Public Administration. The Duke University Award for Rheumatologic and Immunologic Research, 1989. The William Beaumont Award of the American Medical Association, 1989. The academic Excellence Award from Children's Hospital National Medical Center, Washington, DC, 1989. The Surgeon General's Exemplary Service Medal, 1989. The Surgeon General's Medallion, 1989. The 1989 Achievement Award of the American Association of Physicians for Human Rights. The 1989 National Medical Research Award of the National Health Council. The Flame of Hope Award of the Terri Gotthelf Lupus Research Institute, November 2, 1989. The 1989 Maxwell Finland Award in Infectious Disease presented by the National Foundation for Infectious Diseases. The 1989 Helen Hayes Award for Medical Research. The Excellence in Public Service Award of the Committee for the Support of Public Service, May 9, 1990. The 1990 Lifetime Science Award of the Institute for Advanced Studies in Immunology and Aging, Washington, DC. Doctor of Science, Honoris Causa, Mount Sinai School of Medicine, New York, NY, May 18, 1990. Doctor of Science, Honoris Causa, Neumann College, Aston, PA, May 19, 1990. Doctor of Science, Honoris Causa, Georgetown University School of Medicine, Washington, DC, May 26, 1990. Doctor of Science, Honoris Causa, Hahnemann University Graduate School and School of Medicine, Philadelphia, PA, June 1, 1990. 1990 Science Citation Index ranked Dr. Fauci as the eighth most-cited scientist among 1.3 million scientists publishing in the time period 1981-1988. 1990 Humanitarian Award of the Human Rights Campaign Fund Federal Club of Houston. The First International Chiron Prize for Biomedical Research awarded by the Scuola Superiore di Oncologia e Scienze B Biomediche (Genoa) and the Scuola Internationale di Oncologia e Medicine Sperimentale (Rome), 1990. Doctor of Medicine and Surgery, Honoris Causa, Universita di Roma, "La Sapienza," Rome, Italy, 1990. The Fifth Annual Gene Frey Memorial Award for Medicine, The Whitman-Walker Clinic, Washington, DC, November 17, 1990. The 1990 Presidential Award of the New York Academy of Sciences. Fellow, American Academy of Arts and Sciences, 1991. Doctor of Science, Honoris Causa, St. John's University, Jamaica, NY, May 19, 1991. Honorary Fellowship, The New York Academy of Medicine, March 20, 1991. The Award of Courage from the American Foundation for AIDS Research for "extraordinary leadership and personal scientific contributions to AIDS research," December 2, 1991. 1991 Institute for Scientific Information Database Analysis indicated that of the more than 1 million scientists in the world who published in the decade 1981-1990, Dr. Fauci was the 2nd most cited (Nature 355: 101, 1992). Foreign Member, Royal Danish Academy of Sciences and Letters, 1992. Elected to the National Academy of Sciences (USA), 1992. 1992 Sidewalks of New York Science Award from the Big Brothers/Big Sisters of New York City, Inc., New York, May 5, 1992. Establishment of the Anthony S. Fauci, M.D. Perpetual Scholarship by the Sons of Italy Foundation, May 14, 1992. The Cornell University Medical College Alumni Award of Distinction, May 27, 1992. Doctor of Science, Honoris Causa, Long Island University - Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY, June 7, 1992. Honorary title of "Il Commendatore della Repubblica" conferred by the President of the Republic of Italy (awarded 22 June, 1988 in Rome and presented 2 June, 1992 by the Italian Ambassador to the USA in Washington, DC). Election to Fellow, American Association for the Advancement of Science. The Thomas H. Ham - Louis R. Wasserman Award of the American Society of Hematology, December 1992. The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 6, 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service." Visiting Professor of Medicine at a large number of major medical schools throughout the country.

The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 6, 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service."

The Howard University Outstanding Achievement Award, 1993. 1993

Citation Classics (Current Contents) for article - H. C. Lane, H. Masur, L. Edgar, G. Whalen, A. H. Rook, and A. S. Fauci: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. 309: 453-458, 1983. Doctor of Science, Honoris Causa, Medical College of Wisconsin, Milwaukee, WI, May 15, 1993. The R. E. Dyer Lectureship Award, National Institutes of Health, May 19, 1993. Doctor of Science, Honoris Causa, Bard College, May 29, 1993. Doctor of Science, Honoris Causa, Bates College, May 31, 1993. The Humanitarian Award of the Tiro a Segno Foundation, 1993. The Cartwright Prize of Columbia University College of Physicians and Surgeons, New York, NY, November 29, 1993. Doctor of Science, Honoris Causa, State University of New York at Farmingdale, May 19, 1994. Commission of Honor Award, State University of New York at Farmingdale, May 19, 1994. Doctor of Science, Honoris Causa, The University of Connecticut Health Center, Farmington, CT, May 16, 1994. The National Italian American Foundation Award for Special Achievement in Medicine and Science, October 29, 1994. Honorary Fellowship Award, American Academy of Allergy and Immunology, 1995.

Publications:

Dr. Fauci has authored over 850 scientific publications in the field of basic and clinical immunology and infectious diseases.

VACCINE RESEARCH

Mr. PORTER. Thank you, Dr. Fauci. Despite your description of the vaccine for *Haemophilus influenzae b,* last September Science magazine ran an article about vaccine development that indicated that progress has been much slower than expected in producing vaccines for the major diseases identified by an Institute of Medicine report 10 years ago. The article cited the lack of commercial incentives to produce vaccines for illnesses dominant in developing countries, the absence of strong leadership from the many government organizations involved, and the difficulty of the scientific questions.

Do you agree with this rather pessimistic assessment or do you think science is poised to make advances in vaccines in the next few years despite these problems?

Dr. FAUCI. As I told Jon Cohen who wrote the article after he interviewed me for it last year, I disagreed a little with the pessimistic picture that he was painting. Development of vaccines, particularly for diseases as problematic as AIDS and for microorganisms as complex as HIV is by no means simple. It is a very complex, complicated process.

In the same breath, I will say that we are in fact making progress. Last spring, almost a year ago, we made a decision that we were not going to push ahead with a wide scale vaccine trial for one particular type of a vaccine for HIV, gP120, for a number of scientific as well as community-based reasons, such as preparedness for the vaccine. It was that period of time where what I thought was inappropriate pessimism arose, and, actually, stimulated the writing of this article. However, vaccine advances are being made right now. For example, hepatitis A affects 100,000 to 200,000 people a year. We now have a new hepatitis A vaccine. Another example is the *Haemophilus influenzae b* vaccine I spoke of.

Although HIV/AIDS is quite problematic, there are a number of important approaches in the pipeline. We will not have an effective vaccine tomorrow or next month or next year, but I am assuming, and I think correctly so, that by continuing to push in basic and applied research, that we will get a vaccine for HIV and for many of the other diseases that are still scourges of the public health.

Mr. PORTER. It is my understanding that there were two leading vaccine candidates and you decided not to go on to the next phase of trials for either of them.

Dr. FAUCI. Right. They were equally unimpressive.

Mr. PORTER. I also understand that WHO has decided to proceed with further testing of them. Do you think that is a mistake?

Dr. FAUCI. No, because, Mr. Chairman, I made it very clear in my statement to the press after that meeting that this was not just an individual decision of mine. We brought in a number of advisers in a working group that included not only AIDS scientists but vaccinologists who were involved with AIDS as well as members of the community. We then took their advice and brought it before our legislatively mandated AIDS Research Advisory Committee and all came up with the same decision.

The point I underscored was that for HIV infection in this country, given the dynamics of the epidemic, the preparedness of the community, and the incidence of infection, that it would not be appropriate at this time to put a massive amount of resources into a large efficacy trial for those two products. I underscored very emphatically this does not mean that given a different country, like the sub-Saharan African countries or Thailand, which have completely different dynamics of the epidemic you might come up with, on balance, that you should go ahead.

The difficulty we were faced with was that we had a vaccine we did not think would be much more than 30 percent or so effective. And, given the rate of infection in this country and the preparedness of the community, that might not be a good idea. Whereas in a sub-Saharan African country, where you have enormous rates of infection, the balance might tip it the other way towards conducting a trial. So that is the perceived disagreement between ourselves and the WHO, which really is not a disagreement at all.

OFFICE OF AIDS RESEARCH

Mr. PORTER. You have now had experience with a complete cycle of budgeting with the Office of AIDS Research. And what I would like you to do is to describe the process for us.

Do you begin the budget as you would normally but then submit it to OAR for review and comment followed by a pass-back of funding totals and program priorities? How different was your initial AIDS budget from the one that was passed back to you by the OAR, both in total and in areas of emphasis? And has the development of a consolidated AIDS plan by the OAR program led you to change any of the priorities in your AIDS research portfolio? All those questions, and I have two minutes left.

Dr. FAUCI. Well, in the first year, OAR began the consolidated budget. When Dr. Paul took over, he had to jump in right in the middle of the cycle. So we essentially used what we had already prepared.

What we are doing now, with the 1996 budget, and what we are already starting to do vis-a-vis the 1997 budget, is to put in proposals based on a research plan that is formulated, as was described this morning by Dr. Varmus and Dr. Paul. All of the Institutes as well as outside advisers get together and formulate a consolidated plan.

That plan goes back and forth to the Institute Directors and then finally we submit a budget, at multiple levels. It is not as if I will ask for something and get back something less or more. We are asked to submit at a level budget, at a 5 percent increase or X percent increase and then that budget gets put into the formulation of the plan. That budget then comes back to us, according to the plan, with some modifications, and then it goes back and forth.

So it is really an iterative process. Of course there were some differences, as you might expect, from what we put forth in our budget that would ultimately come out in our request, but those, again, were things that were discussed back and forth. Probably the most outstanding one was the amount asked for for clinical trials. I asked for somewhat more than was actually given back. So it was something that was done collegially back and forth.

Mr. PORTER. Mr. Hoyer.

HIV/AIDS INCIDENCE

Mr. HOYER. Thank you very much, Mr. Chairman.

Dr. Varmus, I am sorry I missed your testimony this morning. I am a Ranking Member on another committee and we had the White House before us and their budget, so I apologize.

Dr. Fauci, I don't know whether Dr. Varmus went into this this morning. We have had some sort of debate here, a discussion in the committee, with reference to HIV/AIDS incidence and whether it is decreasing, or whether it is growing. The nub of the argument is whether or not the present situation justifies a flat or a heightened investment in research directed at HIV/AIDS. I would like you to comment on that.

Dr. FAUCI. Sure.

Mr. HOYER. Particularly to the extent that you have knowledge of the CDC figures, which implies a reduction from 100,000 or so down to 80,000, in round numbers, from 1993 to 1994. The hypothesis, then, becomes we have a handle on it so we can divert funding from AIDS.

Dr. FAUCI. We did discuss the numbers and I think everyone agrees now the misunderstanding is now an understanding, and that is that the numbers for 1993 were 106,000. The numbers for 1994 were around 80,000. There was a jump from 1992 to 1993 based on a change of definition in which individuals who do not necessarily have clinical disease but whose CD4+ counts go below 200 automatically get diagnosed as having AIDS. That accounted for the jump from 1992 to 1993.

Then, when the number went down from 1993 to 1994, there were two things that were contributing to that. One was that cases that would have ultimately gotten clinically ill in 1994 were already considered AIDS in 1993. So it looked like there was a major drop when there was not really a major drop.

When you put all those things together, you are seeing what is probably a plateau. But the story does not stop there, because what happens is you get caught up in a numbers game. If the amount of new cases were rising dramatically a couple of years ago, and now they are going up only by a couple of percent a year, then we don't have a problem anymore. That is not the way you approach a devastating problem like HIV/AIDS. And it really relates a bit to what I said about really going after a disease where you have an opportunity to eliminate it like we did with *Haemophilus influenzae b* with the vaccine.

I believe it was Mr. Riggs who asked Dr. Varmus the question this morning, about how do you make a decision of when to put a full court press on a disease? Is it the numbers of people per given year? That is one of the things you consider, but, also, it is the opportunity you have of making an impact, number one; and, number two, it is the dynamics of the disease. If you have a disease in which you are putting a steady amount, even though it is a very devastating disease, you are really almost at a plateau scientifically when you know you are going to get the answer but the answer is going to have to take an unknown number of years to become apparent.

But when you have an infectious disease that is an epidemic that is by no means under control, in fact we are seeing a shift in the demography of AIDS to women, heterosexuals, and children, I think it would be oversimplifying to look at a set of numbers and say because the increase is a couple of percent this year to next year, as opposed to 25 percent a few years ago, that all of a sudden we have to dramatically change the commitment we have to this very devastating epidemic.

That is the way I look at it.

Mr. HOYER. I am pleased that you believe that what was misunderstood is now understood. However, I will tell you that Mr. Istook was with me at Treasury Postal with the White House, and he was the one who had researched this and brought up the question. I made the suggestion in the hearing that you have just made, that the 1992 to 1993 jump was because we included far more people and, therefore, the comparison would be 1992 to 1994 and not 1993 to 1994.

But we need to clear that up, because it is obviously going to have an impact as we mark up this budget as to how we allocate funds within the NIH Institutes.

Thank you very much for your, as usual, very cogent and thorough answer. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Hoyer.

Mr. Miller.

AIDS FUNDING

Mr. MILLER. Thank you. I am sorry I missed your presentation this morning, Dr. Varmus. I had a budget meeting this morning with my Republican colleagues.

I'd like to ask a couple of questions. A question was raised earlier and it has been raised by my colleagues on this side, regarding the justification of the total dollars for AIDS research when we have cancer that is getting more money but not on a per capita basis. You did that a little bit with the one chart. However, I need to be able to justify to my colleagues that same argument. So would you articulate that again? Was that asked this morning?

Dr. VARMUS. It was discussed this morning.

Mr. MILLER. Or maybe you can send me a letter so I can share it with my colleagues. But take a quick second to explain the specifics; I understand the spin-offs.

Mr. HOYER. If you will yield for one second. Ms. Pelosi informs me Dr. Varmus was dynamite. So you and I missed a very good presentation.

Mr. MILLER. I am sorry about that. I don't know who wants to answer the question, then?

Dr. FAUCI. I would be happy to answer from my Institute's standpoint. For example, my Institute has a budget of over a billion dollars and right now, over half of it, 53 percent, is AIDS, HIV/AIDS.

Now, if you say: Wait a minute, you have malaria, you have immunologic diseases, et cetera, are you saying that AIDS is more important than those diseases, or that we should be giving more to those other diseases? I don't think we should look at it that way.

You ask the more global question of cancer versus heart disease versus AIDS. Yes, cancer is a very serious problem. There are more scientific opportunities than we have resources for now with cancer. The same can be said of heart disease, and the same can be said of diabetes, and the same can be said of the other diseases studied in my Institute.

We feel, as scientists, that the amount of money we now have in AIDS is appropriate to the magnitude of the problem and to the opportunity. When we said that at the NIH, I believe it was Mr. Istook who said. Do you mean the scientific opportunities for scientists for your career building? We are not talking about that, we are talking about a point in the evolution of a disease when you have more opportunity than at other times. Not all opportunity here and no opportunity there, but there is a window of opportunity when you can actually make a major impact.

That is really where we are with HIV. So although we are all sensitive, myself included, to the importance of research in other areas, and we are supporting other areas substantially within the constraints of a constrained budget, we feel as scientists and as people in the public health community that that is very well justified.

Dr. VARMUS. I would give one specific example that might be useful to contemplate. In cancer research, we have known for a long time that we are faced with a major problem. But 20 years ago, when the war against cancer began, it was decided to concentrate on a couple of scientific questions that might not have been seen as being directly applicable to lung cancer or breast cancer, two of the major cancers that afflict human beings. Emphasis was placed on cancer viruses of animals and upon some rare cancers like retinoblastoma, a disease that only occurs in a small number of individuals every year. Studies of these apparently small public health problems has led to the revolution in cancer genes that now affects our thinking about all cancers.

So I would argue what was done in the 1970s and 1980s in thinking about how to appropriate money for cancer was to look for those situations in which the opportunity to obtain deeper understanding of the disease was clear and to follow those leads expecting they would lead to a more profound understanding, which has happened.

Mr. MILLER. Do I have time for one more question, Mr. Chairman?

Mr. PORTER. Yes.

PATIENTS AND ROYALTIES

Mr. MILLER. This may relate to Dr. Varmus more, since I missed you this morning. Is there any relationship between the eventual product going to market and what the NIH gets for the research that they contribute towards that?

I remember my undergraduate alma mater, one of our claims to fame—I don't know if you knew this—Gatorade was developed by the football team at the University of Florida. That was why it was called Gatorade. And they received the money or royalties from Gatorade. We had football in the afternoons, and it was hot down there and we had problems with losing body liquid. So it was a shared royalty between the medical school and the football coaches.

Dr. VARMUS. Your university missed a big chance to do the patenting. They ended up getting 1 percent on every dollar thanks to the good heartedness of the inventor, because the university itself had failed to take on the——

Mr. MILLER. Dr. Kaid?

Dr. VARMUS. He was a marine physiologist at the University of Florida.

Mr. MILLER. I don't understand who gets all the money in royalties. I remember hearing all about how AZT was developed by NIH, and whoever has it, Burroughs-Wellcome ends up getting all the money. How does that work? Are we getting the maximum we can?

Dr. VARMUS. The rules differ depending on whether the research is done at the institution to which the NIH has given the grant or whether it is done at the NIH.

So to give you a couple of examples. Under the Bayh-Dole Act, we delegate to our grantees the responsibilities of doing technology transfer and applying for patents on any invention that is made with NIH money at the grantee institution. In contrast, if NIH is involved through the activities of intramural scientists to make an invention, they are allowed to apply for a patent. Returns come to the inventors (the NIH scientists), and to the government, if the returns exceed a certain amount. In that case, the government holds the patent rights.

Mr. MILLER. When was the last time that whole process was reexamined?

Dr. VARMUS. It is undergoing examination all the time. We recently had a series of meetings to examine both our CRADA policy and our so-called sponsored research agreements under the Bayh-Dole Act. We can provide you with reports of those meetings, if you are interested.

Mr. MILLER. I know this area is getting ready to explode over the next decade, as far as applications worldwide in some of the research that is being developed. Are we getting our proportion or a fair share out of it, so that long-term we can keep plowing back into research?

Dr. VARMUS. Well, the returns are not of sufficient magnitude to make a major dent in our research enterprise.

Mr. MILLER. Could they?

Dr. VARMUS. I don't believe so.

Mr. PORTER. Thank you, Mr. Miller.

Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman. Welcome, Dr. Fauci. Welcome back, Dr. Varmus.

Dr. Fauci, thank goodness you are where you are. You give us hope. When I thanked Dr. Varmus this morning for his leadership at the NIH and the excellence of the work there, and for being able to retain and attract such an excellent team, I most certainly was including you high up on that list. Because you have not only done excellent work, you have kept faith to fight the fight, and it has been a long fight. I don't think you had any children when you started this. Now you have a whole lot of babies.

Dr. FAUCI. Eight, 5, and 2. I just want to show my lab that I do come home every once in a while.

INVESTMENT IN AIDS RESEARCH

Ms. PELOSI. At least three times. No, I know your family is very precious to you, but the sacrifice you make is a great one. But as

I said, I thank God every day you are there. I never want to hear that you are not.

Unfortunately, I got into the meeting after you had started your testimony. I know you referenced a question I asked Dr. Varmus this morning about the payoff from the investment in AIDS in terms of other diseases. When I asked Dr. Varmus that question, my colleagues had other responsibilities, as they did when Dr. Sharp was here and he so eloquently put on the record some of the things we have learned from AIDS research, and they are significant. So if you could answer that as well using your chart or whatever.

Dr. FAUCI. I will put it up very quickly and just show it to you. It is right here. The point I was making is that when I started off I spoke about basic research having spin-offs for other diseases. AIDS was one of those diseases. And we really have a repetitive cycle. It happens with a number of diseases.

AIDS is a very good example because of the nature of the research that goes into AIDS, which is microbiology, molecular biology, and immunology. What we are already seeing is that the approach towards understanding the immune system in general has caused our understanding to skyrocket.

So all of the things that go into the immune system and immune system diseases, be they autoimmune diseases, organ transplantation or a variety of other diseases, we understand better. If you look at antivirals that have an affect on viruses that have nothing to do with AIDS, our ability to be able to target antimicrobials to viruses has improved greatly. So has our understanding of other sexually transmitted diseases and new approaches to vaccines. This is very important. Therapies for opportunistic infections are improving.

For example, the day after tomorrow, in the New England Journal of Medicine, two articles will appear on prophylaxis against pneumocystis using a variety of drugs and showing what a major impact that has had on HIV-infected individuals. And the next article in that journal describes the major impact of fluconazole for fungal infections such as Cryptococcus and Candida, as a major impact.

When people have breast cancer or colon cancer and they get immunosuppressed by therapies to wipe out the cancer, they will be in an immunosuppressed state similar to that of HIV-infected individuals. The fact that we know how to treat those diseases so immediately is going to have an impact on diseases such as a variety of cancers. That is really the point I was making.

NIAID BUDGET DECISIONS

Ms. PELOSI. I thank you very much because you have shed light on the issue even more specifically than we had on the record.

I wish we could take a more holistic approach to the fact that all of this research benefits everyone and that the exposure that the human body has benefits from all of any work you do on the immune system and some of the other aspects that you mentioned.

I remember one time my colleagues and I were in a hearing when Dr. Fauci was there at Government Operations, and one of our Republican colleagues, who had not been supportive himself in the past, had allergies. When he went to NIH and saw the work on AIDS, because we were talking again about the immune system, he saw that he was served well with his allergies because of the work that was done on AIDS. Of course, that opens up a whole other area of benefit that many people are familiar with, who may not ever have any cause, hopefully, to have any familiarity with HIV.

Dr. Fauci, I wanted to ask you a budget question and it may be repetitive of what our Chairman has already asked you. Forgive me if it is. Could you outline how you go about the process of putting together a budget request and how issues like AIDS or autoimmune disease or Lyme disease or asthma may be given priorities in a budget?

Dr. FAUCI. What we do in our Institute, Ms. Pelosi, is we have a series of events that take place that are timed with the budget cycle. The centerpiece of that, in conjunction with input from our ad hoc groups, our constituted councils, like our National Advisory Allergy and Infectious Diseases Council, are two major retreats where we take the executive committee and selected people from the Institute and go away for a day and a half or two days. We usually go to Annapolis, Steny, sort of stay in your area.

Mr. HOYER. Good judgment.

Dr. FAUCI. We take a policy look at the broad scope of what the scientific opportunities are and we look at the balance in HIV versus transplantation versus asthma, et cetera. Also balancing what is more appropriate to do intramurally versus extramurally.

Then, in the summer, we take that framework that we developed and we look at individual projects, what is right for something like a request for applications how much should we be putting in to pure investigator-initiated work and how much of basic work is right to go toward AIDS versus another disease. And then when we submit our budgets to Dr. Varmus and to Dr. Paul in the OAR, what we do is use that planning process to essentially insert it into the broader planning process Dr. Varmus has for the whole NIH and that Dr. Paul has established for the OAR.

BLOCKING HIV TRANSMISSION

Ms. PELOSI. I appreciate that. Thank you. I will ask one more quick question.

What progress, Dr. Varmus, has been made in the last year in research on ways to kill HIV and other transmitted diseases that are potentially dangerous to women? Like microbicides.

Dr. FAUCI. As you know, since we have discussed this several times, I will mention it very briefly. We have a major effort now in topical microbicides which are going to have an impact. We are at the basic science and product evaluation stage, and then we are going to move into the clinical trials component, in which we are looking at blocking not only HIV but other sexually transmitted diseases.

As you well know, other genitally erosive sexually transmitted diseases, particularly in women, lead to a much heightened probability of transmitting HIV infections. So we will have a double advantage not only of blocking certain sexually transmitted diseases that have a terrible negative impact on women as well as fetal wastage and chronic pelvic inflammatory disease, but also cut down on the probability of transmission of infection. That is in the area of sexually transmitted disease and topical microbicides.

In addition, in our broad net of clinical trials, including the ACTG, the community program, the intramural program, et cetera, we have, since the late 1980s, gone from women being 3.8 percent of the participants in the clinical trials up to about 14 percent now. We have actually gotten up to the number that is the relative proportion of women who are HIV infected. We have made a lot of progress since the late 1980s and early 1990s on that.

Mr. PELOSI. I appreciate, in closing, Mr. Chairman, Dr. Fauci's leadership, the excellence of his work and the hope he gives us. It is clear to see why in the 1988 campaign in the debates when President Bush was then Vice President, Vice President Bush was asked to name a person who was his hero. He named Dr. Fauci. I want to remind those who remember and also to mention for those who may have missed it, it is clear to see from your fine work why the President would have said that. You are our hero, too. Thank you, Dr. Fauci.

Dr. FAUCI. Thank you very much.

Mr. HOYER. This is a tough hearing on you, Doctor.

Mr. BONILLA [presiding]. Tough hearing. And it is not over.

Dr. VARMUS. He is a Republican hero.

Mr. BONILLA. But seriously, I was going to start out with a compliment, Dr. Fauci. I just coincidently saw you on some network evening newscast recently, when there was information about the new protein you are using to combat AIDS. You are very well spoken, you are a great representative for NIH in the community, and I would encourage you to keep doing that because the more the population out there understands what you are doing and what everyone at NIH is doing, the easier our job is going to be in appropriating funds for what you are working on. So you are doing a great job and I am not surprised to hear what my friends——

Mr. HOYER. Would the Acting Chairman yield?

Mr. BONILLA. Absolutely.

Mr. HOYER. Let us not try to undermine his retirement program, however, in the next few days.

AIDS DRUGS

Mr. BONILLA. Thank you, Steny.

I would like to start out, Dr. Fauci, by asking about NIAID's involvement, if there was any, with the drug known as MK–639 developed by Merck, which some say works better and is better at inhibiting the AIDS virus than AZT, and does so without side effects. So tell me about that.

Dr. FAUCI. Well, I will take the last part of the statement first. Mr. Bonilla.

There is no drug that is without side effects, so we have to be careful about that. There will always be side effects when you have drugs that require a certain amount of effect on processes such as inhibiting an enzyme like protease. But relatively speaking, we do not see some of the toxic side effects that make AZT intolerable with this particular class of drug.

The Merck drug and other drugs that use the inhibition of a very important enzyme the virus needs to cleave the proteins that allow it to become what we call the virion, or a whole virus, has an enormous impact on the level of virus in an HIV-infected individual. The level of virus drops by sometimes a hundredfold.

One of the difficulties one faces is that the virus has the uncanny ability, because of its high replication and mutation rate, which means it divides very fast and it changes as it divides, is that it can escape or become a mutant that will be resistant to drugs. The strategy now is to use those classes of drugs, which are very potent, in combination with other drugs to try to create a situation where the virus will be unable to effectively mutate.

The reason why the protease inhibitors are so important is that they are extraordinarily powerful but they do have difficulty in that they induce resistance reasonably rapidly. But I believe that is a price we are going to have to face in any drug against a microorganism that has such great mutational capability. But it is good news. I am giving you a caveat because we have been in a situation too often with HIV that when a drug comes out we think it is the answer. It is an important step in the armamentarium we will use along with other antivirals, including some of the immune enhancers. So I think it is an important step forward.

ASTHMA

Mr. BONILLA. A question now about a study recently that Prudential announced, a program designed to improve the treatment of asthma. They stated that the program was based upon a report by the Heart, Lung, and Blood Institute which issued new guidelines for the management of asthma. However, according to Prudential, the guidelines were published in a lengthy document that did not prove to be a quick reference for primary care providers. And we all know they have a ton of paperwork to deal with just in terms of running their office. Did NIAID have a role in this report and can you explain why that report was not more user friendly?

Dr. FAUCI. Is Claude here? No. We did not have a major role in the report. And I agree the report is not particularly user friendly. It is very complete and I think what we will be seeing distillations of it.

In fact, in some of the reviews we write, and even in a textbook I am involved with, I am going to take and distill that lengthy report to about two pages so people can just open the book and take a look at it. It is an excellent report, but you are right, it needs to be distilled down to be more user friendly. It is already being done. Some of the review articles in places like the Annals of Internal Medicine and the New England Journal of Medicine are excerpting from the report, making it more user friendly. But out of necessity because they wanted to be complete, it was a rather lengthy report.

Mr. BONILLA. Like Cliff notes, then, right?

Dr. FAUCI. Indeed.

OUTREACH TO MINORITIES

Mr. BONILLA. In your testimony you talk about the inner-city asthma study, which I presume would focus more on inner-city kids, primarily on African Americans, and that is good. In your budget justification it states that NIAID will establish a series of asthma outreach and demonstration research grants. What research and outreach is being done in the Hispanic communities, and other minority communities as well?

Dr. FAUCI. As a matter of fact, a very important part of our national cooperative inner-city asthma program is targeted at African Americans and Latinos, as well as to a lesser extent, Asian Americans. In fact, outreach is an offshoot of the original projects, which tried to identify what the factors were in the increased morbidity and mortality among African Americans and Spanish-speaking minorities. The program has now reached the phase where the outreach to the community has a component of the research using what Phase I was able to establish. So we are well on the way. In fact, it is a totally integrated important part of the program for the Spanish-speaking minorities in those inner cities.

Mr. BONILLA. I have a series of questions that are kind of lengthy that I will submit regarding grants that NIAID administers. If you would be so kind as to respond for the record, I would appreciate that.

Dr. FAUCI. Be delighted to.

Mr. BONILLA. Thank you, Doctor. Chairman, I yield back.

Mr. PORTER. Thank you, Mr. Bonilla.

Mr. Stokes.

Mr. STOKES. Thank you. Mr. Chairman, as you know, this morning I was called away to the Rules Committee. I had a number of questions for Dr. Varmus and I would like to put those questions in the record, if I may.

Mr. PORTER. You can ask them now if you want.

EMERGING INFECTIONS

Mr. STOKES. Well, I want to ask some questions of Dr. Fauci. I happen to be one of his admirers. Dr. Fauci, you are in good shape with me, too.

In your opening statement you focused on reemerging infectious diseases. Also during last year's hearing, you emphasized this health problem as well. Recently, there has been a lot of interest on this subject. Release of the book Hot Zone, and the new movie coming out entitled "Outbreak" have also added to the increased interest. In your professional judgment, what type of strategy is needed and would be effective in addressing infectious disease outbreaks, and, more importantly, tell us to what extent they can be prevented.

Dr. FAUCI. Right. There are a number of strategies. The NIH, in its mission, is a very important part of one of those strategies. When you are talking about diseases that are truly new in the sense of when HIV first came upon us and diseases that are reemerging, such as the Hantaan virus or TB even in its reemergence, there are a couple of ways that you can approach that. One of them is more of a surveillance approach, which is more the mandate of the Centers for Disease Control, a very important part of it. There is another indispensable part in which the NIH plays a major role, and that is the point that I emphasized in my opening oral statement. That is, that fundamental basic research in microbiology and immunology is absolutely essential to position us to be able to move quickly when we are confronted with a here to for unrecognized microorganism. That is exactly the argument for why we must maintain that fundamental base of basic research.

It applies to all Institutes, but in our situation, with infectious disease, it has to do with microbiology, general infectious disease, and immunology. I would submit to you that that is the short answer for what the NIH plan is, to continue to be very attentive to the fundamental tenets of basic research in those disciplines.

MINORITY PROGRAMS

Mr. STOKES. Doctor, as you know, I have been pleased with the results of the evaluation of your Institute's introduction to biomedical research program, which provides students from underrepresented minority groups an orientation to biomedical research careers. Is that program still underway, and to what extent is it being replicated across the Institutes, the Centers, and the Divisions of NIH?

Dr. FAUCI. We are proud to say, Mr. Stokes, that it is still alive and well and growing. The response that we have had from the students is good. As you know, when something is good and it works, the word spreads. We are having a very gratifying response to that program. Other Institutes are also beginning to implement similar types of programs.

EXCESSIVE ANTIBIOTICS

Mr. STOKES. Recently, the media has been giving increased attention to the excessive use of antibiotics. What is the extent of this health problem? Tell us, what are the implications of the problem, especially as it relates to the reemerging infectious diseases? Also, what precautions must be taken relative to this?

Dr. FAUCI. The answer to the fundamental question you are asking, Mr. Stokes, is that it is, in fact, a problem. It is a problem I think that is a reflection of a number of things. One of them is the general atmosphere in the delivery of health care, where it is of great concern to miss something and make a mistake. I think that has to do with everything from the litigious nature of our society to the real concern that you are going to miss something important.

But the overuse of antibiotics is in fact a problem. With the inappropriate use of antibiotics in some cases, what you have, not infrequently, is the enhancement of the emergence of resistant microorganisms. A microorganism that you have known about for decades now becomes resistant to an antibiotic. This microorganism could be as devastating as a microorganism that you never heard of before. That is the major negative consequence of inappropriately using antibiotics.

Another important one is that you increase the incidence of drug reactions, which are also an important public health problem when you think of the millions of doses of antibiotics that are given per day. So it is a problem. The solution to the problem, I think, is greater education of the caregivers about the importance of treating appropriately when you should treat but also hold back when there is not a good reason to treat.

We need to constantly address that in our guidelines to different types of therapies for various diseases. It is not going to be easy, because the knee-jerk reaction of some people is to prescribe an antibiotic over the phone without even seeing the patient. That is something that sometimes is good because it can be lifesaving, but more often than not it is inappropriate.

ASTHMA RESEARCH PROGRESS

Mr. STOKES. This is my last question. Asthma continues to be a major medical problem affecting some 10 million Americans, and more than one-third of whom are under 18 years of age. Last year, you indicated recent studies revealed that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. Are we making any measurable progress in this research area, and what can you tell us this year that you could not tell us last year about this health problems?

Dr. FAUCI. Yes, actually there are some very simple things. The answer to the question you are posing is quite correct, that there is a disproportionate burden on African Americans and Hispanics in inner-city areas. Some of the biological reasons may still be elusive but some practical reasons have been identified and that is, for example, particularly in certain of the crowded living quarters in the inner-city areas there is an increased allergic response to cockroach products, believe it or not. That has been identified as an important inducer of severe allergic reactions in the upper airway that lead to an asthmatic attack for people who have a susceptibility to asthma.

So the outreach that we are now implementing as a part of the second phase of that program vis-a-vis desensitization and education are aimed at something as simple as that. We work more intensively on some of the more complex potential biological problems that people might have that make them more susceptible.

Mr. STOKES. Thank you, Dr. Fauci. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Mrs. Lowey.

AIDS FUNDING

Mrs. LOWEY. Thank you, Mr. Chairman.

Thank you for being here, Dr. Fauci. I understand, and I apologize for being late, that there were questions asked concerning sexually transmitted diseases. I will, therefore, just introduce some additional questions for the record, and I would be most appreciative of your response.

Regarding AIDS funding, there has been considerable debate about the appropriate level of funding for AIDS research in this committee. Could you give the committee your professional opinion of whether it is appropriate to compare dollars for AIDS versus other diseases in one fiscal year, given that AIDS research is a fairly new field? In other words, there are other diseases that have been receiving funding for many, many years and, therefore, the comparison may not be appropriate. Could you comment on that?

Dr. FAUCI. Yes, I actually answered that question but I will give you a short version of it.

Mrs. LOWEY. Okay, thank you.

Dr. FAUCI. I don't think it is appropriate to make that the sole parameter. Certainly you need to look at burden of cases as one part of the equation. But I feel extremely uncomfortable in going and rigidly adhering to just numbers when you have various diseases, particularly an infectious disease, that is an epidemic, in which the dynamics of an epidemic are clearly different from one year to another and there are windows of opportunity through which you could have a major impact.

One example I alluded to was the window of opportunity we had with essentially eliminating *Haemophilus Influenzae* B. Because the opportunity was there, we put, as I called it, a full court press on it. That is where we should be and are right now with HIV. A full court press is justified.

TUBERCULOSIS RESEARCH

Mrs. LOWEY. Thank you very much. I am sorry I missed the other question before.

I also see in the budget justification that the budget targets an increase of $1 million for basic research in tuberculosis pathogenesis.

Number one, I would appreciate it if you could discuss with the subcommittee the reemergence of TB. Why are we seeing this reemergence? Did our years of disinvestment in TB make us lose ground?

And with regard to TB and AIDS, you will recall we met a few months ago to discuss the CPCRA, and I understand that NIAID has recently funded a program in Uganda to look at TB infection in AIDS patients. NIAID has an existing relationship with two New York sites which are second and third in the Nation in recruiting TB patients for AIDS trials. Why do we need to spend our money in Uganda when we have existing patients in this country whom we could recruit for this type of research?

Dr. FAUCI. It is a good question with many answers. I will go to the generic question of tuberculosis. Tuberculosis reemerged not because of any slacking off of a scientific effort. The slacking off of the scientific effort put us behind in our approach to the reemergence of tuberculosis. Tuberculosis reemerged because of a variety of socioeconomic as well as the most important factor, the emergence of the HIV epidemic.

There was a baseline level of tuberculosis that was essentially going down in the community. Fundamentally it was in inner-city areas, but nonetheless diffuse in some respects. When we got to the mid-1980s, many of the people who were HIV infected also had tuberculosis that was latent. When their immune systems became suppressed they had reactivation of tuberculosis, which then spread around the community. So it was reactivation in people who were otherwise containing a latent infection well, which spread to others.

We saw a plateau in the mid-1980s and then we saw it starting to come up. When we started to see a plateau, we moved money from other areas into tuberculosis. Then we requested a major input and that the committee granted us so we now have, in our Institute alone, $32 million in tuberculosis research when back in the mid-1980s it was about $1 or $2 million or even less. There has been an extraordinary escalation here again, which refers to what I said about window of opportunity.

With regard to the CPCRA and its ability to have an impact on tuberculosis, that is indeed a very complex problem. I would be happy to discuss this in detail with you, whether or not a CPCRA got funded because it did not do well in peer review.

The whole question of the clinical studies we do in TB are very problematic in the populations in the cities we are dealing with. Those individuals never even get into a CPCRA long enough to be in a clinical trial. That is a reflection of the health care delivery system, not of the CPCRA.

We need to rethink all of the approaches we are having towards tuberculosis. I think to compare that to sub-Saharan Africa really is in some respects apples and oranges. It is not, why aren't you doing it in inner-city New York and why are you putting all the money in sub-Saharan Africa. It is much easier to do a study. In fact, it is possible to do the study in a sub-Saharan African country because of the rate of infection in Africa. It has been very problematic even with the CPCRA, to do it in inner-city New York. Even if they got funded I don't think we would be able to do the study very well.

Mrs. LOWEY. Let me just say we have been through this before so perhaps we can——

Dr. FAUCI. And you are still smiling at me, which is good.

LYME DISEASE

Mrs. LOWEY. As you know, I have great respect for the work that you do and the Institute does. So hopefully I will continue to smile and we can discuss it.

Concerning Lyme disease, your budget states that you will establish a framework for starting a clinical trial for improved therapy of late stage Lyme disease. Likewise, in your testimony, you mentioned a large scale test currently being conducted on Lyme disease vaccines. Could you discuss where we are on Lyme disease research? How far do we have to go with appropriate prevention and treatment? I am particularly interested in the test because a member of my family suddenly found out that they tested positive. So she is going for some more tests, so I am interested in the testing, the prevention, and the treatment.

Dr. FAUCI. Starting off with the testing first. When you are talking about acute Lyme disease, it is pretty easy to make the diagnosis if you think about it. You have a certain profile of an antibody response that is pretty characteristic. When the symptoms are classic, you treat it. The antibiotic treatment is highly effective. That is not a problem.

The problem with treatment is in the situation when you are in an endemic area, like your area, and you have people who have either chronic Lyme disease or something that is mimicking chronic

Lyme disease, you do a serological test or a test for antibody and the results are very ambiguous. You do not know if the results are really positive or are a reflection of the fact that you have been living in that area for a long period of time.

I alluded to the test we have developed in my opening statement. We are directing a study of making a diagnosis in someone who has chronic disease and for whom you cannot make a definitive antibody test. Particularly for people who have serious joint involvement, we take a small bit of tissue and do a PCR analysis for very, very small amounts of the Lyme disease microorganism. If we can identify that individual as truly having Lyme disease, we then do a clinical trial of a particular combination of antibiotics.

The stumbling block with Lyme disease has been the lack of ability to definitively diagnose the chronic stage and the fact that the symptoms can be so vague in the chronic stage that they get confused with a variety of things, including chronic fatigue syndrome.

Mrs. LOWEY. How did you guess what my next question was?

Dr. FAUCI. I knew that.

Mr. PORTER. The trouble is you have run out of time.

Mrs. LOWEY. That was very kind. You knew I was running out of time.

Mr. PORTER. Go ahead and ask the last question.

CHRONIC FATIGUE SYNDROME

Mrs. LOWEY. Thank you, Mr. Chairman. I was just going to ask—I have had a large constituency come talk to me about chronic fatigue syndrome, as you know, and I was really very interested in the recent discoveries. So perhaps you can enlighten us all about this discovery. Are we close to understanding this disease?

Dr. FAUCI. Chronic fatigue syndrome? I don't think we are. We may be very close but we do not know that we are close, that is the problem. The information we have now, I think, does not bring us much closer.

We have redefined the definition of chronic fatigue syndrome to categorize it so we can have a group of people that we feel confident fall into this category. Then we can do a number of diagnostic tests on them to determine if we can get a clue as to even what major organ system is involved. I can assure you, as I have assured the committee in previous hearings, that we are committed to finding the solution to this.

Mrs. LOWEY. Thank you for your indulgence, Mr. Chairman.

Mr. PORTER. Thank you, Mrs. Lowey.

Ms. PELOSI. Mr. Chairman.

Mr. PORTER. Ms. Pelosi.

Ms. PELOSI. Mr. Chairman, may I take a few seconds to comment on something Mrs. Lowey said about the Uganda issue, and that is——

Mr. PORTER. I would never prevent you from commenting on anything.

INTERNATIONAL HEALTH

Ms. PELOSI. Oh, yes you have. But the Chairman is most generous.

When I came into the room, Dr. Fauci was responding to your question about the World Health Organization. I just wanted to take a moment to say that we do, as a country, have a responsibility internationally on the AIDS issue as well.

Certainly Representative Lowey is correct that we have to do research to benefit our own people, but I think that we all see how important the international effort is, both in terms of research and that it is just going to swing right back and hit us if we are not looking beyond our own borders. That is why we have over a $100 million which our Chairman, once again, helped us obtain in our other committee that we share service on, the Foreign Operations Committee.

I think we have to recognize, because of the greatness of our country and the scientists that we have here, the world is looking to us for an answer. Thank you, Mr. Chairman.

Mrs. LOWEY. I just want to clarify, Mr. Chairman.

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. I certainly share my colleague's concerns and I agree with her.

Ms. PELOSI. I know that.

Mrs. LOWEY. I wanted to point out there happens to be a little part of New York where we can do some very good research in that regard.

Ms. PELOSI. I understand that.

Dr. FAUCI. I was born there.

Mrs. LOWEY. Thank you.

NIH BUDGET REQUEST

Mr. PORTER. Thank you, Mrs. Lowey.

Dr. Varmus, I have a question for you, if I may. Does the budget we have before us differ for NIH in any way from the budget that you submitted to OMB?

Dr. VARMUS. I would have to look. I think there are some very small differences. I think it depends on when it was submitted. As you know, there was——

Mr. PORTER. Originally submitted to OMB.

Dr. VARMUS. We submit our budget first to the Public Health Service and then to the Department and then the Department forwards our budget to OMB.

Mr. PORTER. Well, let me ask you——

Dr. VARMUS. I am not sure which iteration of the budget you are referring to.

Mr. PORTER. If you would submit for the record and to us a copy of the budgets submitted originally to the Public Health Service, then to the Department and then to OMB.

Dr. VARMUS. I have that information. The budget that was submitted by the Department on our behalf to OMB was slightly less than the President's Budget, by about $16 million.

Mr. PORTER. I am not so much interested in the total as I am in the details.

Dr. VARMUS. Okay.

Mr. PORTER. If you could submit that.

Dr. VARMUS. We will supply that for you.

Mr. PORTER. Appreciate having it.

Dr. VARMUS. Sure.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH
FY 1996 Budget Progression
NIH Spread of Budget by Institute

(Budget Authority in thousands)

	FY 1996			
Institute/Center:	Agency Req. (Appeal) to PHS	PHS Request to DHHS	DHHS Request to OMB	Pres. Budget Request
National Cancer Institute	$2,179,913	$2,053,276	$1,996,912	$1,994,007
National Heart, Lung & Blood Institute	1,380,057	1,298,414	1,296,653	1,279,096 *
National Institute of Dental Research	180,076	168,156	167,758	168,341
Nat'l Institute of Diabetes & Digestive & Kidney Diseases	803,159	755,335	750,594	748,798
National Institute of Neurological Disorders & Stroke	693,289	646,097	645,280	648,255
National Institute of Allergy & Infectious Diseases	608,784	562,608	556,225	557,354
National Institute of General Medical Sciences	969,249	910,571	910,350	907,674
Nat'l Institute of Child Health & Human Development	568,327	533,156	530,087	526,177
National Eye Institute	318,283	299,306	298,899	300,693
National Institute of Environmental Health Sciences	302,133	284,150	278,292	278,832
National Institute on Aging	476,009	445,602	443,881	445,823
Nat'l Inst. of Arthritis & Musculoskeletal & Skin Diseases	251,756	234,883	234,170	235,428
Nat'l Inst. on Deafness & Other Communication Disorders	182,968	171,471	171,352	172,399
National Institute of Mental Health	604,707	561,699	559,314	558,580
National Institute on Drug Abuse	319,900	299,376	299,003	298,738
National Institute on Alcohol Abuse & Alcoholism	201,120	187,699	186,994	185,712
National Institute of Nursing Research	55,226	50,637	50,006	50,159
National Center for Research Resources	334,546	313,440	317,109	316,544
National Center for Human Genome Research	188,590	172,516	166,932	166,678
Fogarty International Center	15,798	14,371	15,826	15,267
National Library of Medicine	161,128	145,016	133,698	136,311
Office of AIDS Research	1,575,903	1,451,674	1,407,893	1,407,824
Office of the Director	261,826	242,951	227,948	230,256
Buildings & Facilities	199,939	143,539	144,370	144,120
TOTAL, NIH Budget Authority	$12,832,686	$11,945,943	$11,789,546	$11,773,066

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* Excludes $15.36 million transferred to HRSA for the National Bone Marrow Donor Program.

NATIONAL INSTITUTES OF HEALTH

FY 1996 Budget Progression

NIH Spread of Budget by Mechanism

(Budget Authority in thousands)

PROGRAM	FY 1996			
	Agency Req. (Appeal) to PHS	PHS Request to DHHS	DHHS Request to OMB	Pres. Budget Request
Research Project Grants	$6,812,139	$6,301,326	$6,263,122	$6,228,660
Number of New RPG's	*8,130*	*6,050*	*6,182*	*6,046*
Total RPG's	*25,867*	*23,787*	*23,737*	*23,874*
SBIR/STTR Grants	182,265	172,854	173,788	194,087
Research Centers	1,144,647	1,087,230	1,029,560	1,033,720
Other Research	574,984	549,074	539,652	543,356
R & D Contracts	914,583	853,322	824,271	802,793
Research Training	428,709	385,814	386,976	390,890
Number of Trainees	*14,931*	*14,123*	*14,248*	*14,541*
Intramural Research	1,333,032	1,289,379	1,269,905	1,272,019
Research Management & Support	533,134	517,688	521,077	520,824
Disease Control/Construction	241,780	225,328	244,418	245,270
National Library of Medicine	164,739	148,439	136,860	139,473
Office of the Director	302,735	271,950	255,547	257,854
Buildings & Facilities	199,939	143,539	144,370	144,120
TOTAL, NIH Budget Authority	$12,832,686	$11,945,943	$11,789,546	$11,773,066

AIDS CLINICAL TRIALS GROUP

Mr. PORTER. Dr. Fauci, your AIDS clinical trial group is up for recompetition in 1996. You have been quoted as saying that 9 to 13 of the units will lose funding. It has been speculated for some time that ACTG would be downsized to free up funding for other priorities identified in the OAR plan. Where is the money being shifted to?

Dr. FAUCI. The money will fundamentally be shifted to the investigator-initiated basic research line. One of the questions that was asked was about the back and forth between the iterations of the OAR and my Institute. As I mentioned to you, the area where there was some difference was what we requested $68 million for the ACTG. They will get $60 million according to the plan. Most of that $8 million will go towards the fundamental basic research pool, or RO1s.

Mr. PORTER. The last time the ACTG was recompeted there was quite a bit of political pressure to continue existing sites. Do you expect similar problems in 1996?

Dr. FAUCI. I expect to have a very busy year in 1996, Mr. Chairman, because when you out of necessity in peer review phase out 9 to 13 units, as you might imagine there will be a lot of fireworks around.

Mr. PORTER. I have two quick questions. Should we destroy the last remaining stocks of the smallpox virus?

Dr. FAUCI. I have been asked that by a number of groups and my short version of it is that, no, that we should not. We could go into a lot of reasons why, but my answer is no and I would be happy to explain that at a later time.

AIDS CAUSED BY HIV

Mr. PORTER. This may not be as quick a question, but do you believe that there is any scientific basis for the arguments advanced by Peter Duesberg and his followers that HIV does not cause AIDS.

Dr. FAUCI. No.

INTRAMURAL RESEARCH PROGRAM

Mr. PORTER. Getting short answers.

Finally, and here is a home run question for you. In last year's outside review panel report on intramural research, your Institute's intramural program was singled out for praise. Can you describe for us some of the management approaches you use to ensure the quality of your intramural research program?

Dr. FAUCI. Well, over the last several years we have paid a very strong amount of attention to the review process. We bring in the best outside reviewers that we can find. We ask around more than just within our own little circle, about who the best people would be. We bring them in and we stringently review the laboratories, but, most importantly, we act on the recommendations of the outside reviewers. If a laboratory is reviewed and individuals are, in fact, evaluated as not being as productive as we feel they could or should be, and if that looks like something that is not correctable, we make resource changes that back up the review. We take it very seriously. I think that has been very good for the Institute because we now are left with a group of investigators who can be defended anywhere, any time, anyplace. That is really the secret of it.

And the NIH, under Dr. Varmus' leadership, has been making that a very uniform type of review so that virtually every Institute will have a uniform review process that will be quite stringent. I think you will see things become even better in the years to come.

Mr. PORTER. We have Dr. Olden and the NIEHS budget to consider next. Does any member of the subcommittee have any additional questions for Dr. Fauci?

Mr. STOKES. I have a number of additional questions I will submit for the record, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Mr. PORTER. Well, Dr. Fauci, we think you are doing a marvelous job for our country, for NIH, for humanity and we commend you for your wonderful work and thank you for being here to testify today.

Dr. FAUCI. Good to be here, thank you, Mr. Chairman.

[The following questions were submitted to be answered for the record:]

AIDS CLINICAL TRIALS

Mr. Porter: Identify FY 1994 - FY 1996 funding for adult and pediatric AIDS clinical trials and their numbers.

Break out the AIDS Clinical Trials Group separately.

Dr. Fauci: The following is a break out of our AIDS clinical trials budget, including the AIDS Clinical Trials Group (ACTG), for fiscal years 1994 through 1996 for adults and pediatrics:

	FY 1994	FY 1995	FY 1996
Adult	$151,196,000	$149,473,000	$149,380,000
Pediatric	44,893,000	46,195,000	48,043,000
Total	$196,089,000	$195,668,000	$197,423,000

It is important to note that a number of our awards provide support for both adult and pediatric studies. The total number of awards for 1994 is 164. The estimated number of awards are 164 and 157 in fiscal years 1995 and 1996, respectively.

The following is the budget for both the adult and pediatric ACTG clinical sites, including the costs for the Operations Office, and for Statistical Data and Analysis for fiscal years 1994 through 1996.

	No.	Amount	No.	Amount	No.	Amount
Adult	35	$ 67,399,000	35	$ 67,399,000	22	$ 60,000,000
Pediatric	22	34,494,000	22	34,494,000	22	34,494,000
Total	57	$101,893,000	57	$101,893,000	44	$ 94,494,000

CHRONIC FATIGUE SYNDROME

Mr. Porter: Please provide a brief listing of the intramural and extramural research projects you currently fund related to chronic fatigue syndrome, including any that are funded through the small grants program.

Dr. Fauci: NIAID's support for Chronic Fatigue Syndrome (CFS) research continues to grow and is expected to reach $4.4 million by the end of FY 1996. We are studying this illness from various angles including immunologic, virologic, neurologic, endocrinologic, physiologic and behavioral aspects, as well as trying to elucidate if there is an etiologic agent involved. The NIAID supports three Chronic Fatigue Syndrome Cooperative Research Centers that conduct research on:

Clinical Research in CFS
Developmental Research in CFS
Quantification of Fatigue in CFS
Allergic Inflammatory Reaction in CFS
Neurophysiologic Disturbance in CFS
Neuropsychiatric Features of CFS
CFS, Fibromyalgia and Depression
Cytokines and CFS
Classification of CFS Patients

Virology Assessment of CFS Patients
Immunological Assessment of CFS Patients

The NIAID also supports various other research projects on Chronic Fatigue Syndrome. These include:

Pathogenesis of Epstein Barr Virus Infections
JHK Virus Study
Exertion-Induced Cytokines in Chronic Fatigue Syndrome (CFS)
Motor Control & Cytokines in CFS
Exercise Intolerance in CFS
Mechanisms of Immunologically Mediated Fatigue
Social Processes & Somatization - The Course of CFS
Virology & Immunology of CFS
Chronic EBV Infection & Chronic CFS

Mr. Porter: Does the NIH CFS coordinator have Institute-wide authority to coordinate budgetary issues and advisory council activities related to CFS? If not, what role does the NIH coordinator play?

Dr. Fauci: Each Institute in the NIH has a specific mission to support research and research manpower development for particular aspects of human health, receives a specific budget from the Congress for that purpose, and uses advisory bodies appropriately constituted for that mission.

In 1991, at the request of Congress, an NIH Coordinator for Chronic Fatigue Syndrome was appointed. Dr. William Raub, Acting Director, NIH, named Dr. John R. La Montagne, Director, Division of Microbiology and Infectious Diseases, NIAID. Dr. La Montagne also serves as the NIH-representative to the DHHS CFS Interagency Coordinating Committee where he is currently co-Chair with Dr. Philip R. Lee, Assistant Secretary for Health, DHHS.

Through the NIH CFS Coordinating Committee, the NIH CFS Coordinator: (1) Facilitates communications among NIH Institutes regarding intramural and extramural activities, (2) Provides accurate reporting regarding NIH CFS research activities within DHHS as well as to Congress and constituency groups, (3) Facilitates development of informed policy regarding assignment and review of CFS research applications, (4) Enhances sharing of multidisciplinary expertise in the formulation of recommendations regarding NIH CFS extramural programmatic activities, (5) Assists in development of complementary research programs which minimize overlap, (6) Provides NIH-wide awareness of CFS research needs and policy issues, and (7) Conveys information between the DHHS CFS Interagency Coordinating Committee and the NIH Institutes.

RESEARCH CENTERS

Mr. Porter: In your half a billion dollar Non-AIDS budget, you support only three research centers. This is well below the average for the typical Institute. Why have you chosen to organize your research mechanisms this way? Have you received pressure from the extramural community to increase your use of the centers mechanism?

Dr. Fauci: We have not received pressure from the extramural community to increase our use of the centers mechanism. To the contrary, we have been encouraged to move away from large, multi-site mechanisms. Due to the significant resources required to support organized research efforts of multiple investigators, we have made a conscious effort to utilize cooperative agreements in support of such activities. This allows for direct participation of our staff in managing and directing research activities that we have resources invested in. In doing so, we achieve the benefits derived from a multi-component attack on research problems or diseases that have traditionally been supported through the centers mechanisms. An added benefit is that direct staff participation permits us and the grantee to respond more rapidly to changes in research direction.

One example is our Cooperative Research Centers for Asthma, Allergic, and Immunologic Diseases, that we had previously supported through the centers mechanism through Fiscal Year 1992. In Fiscal Year 1993, we re-competed these centers as cooperative agreements. In this case we believe that not only has the research benefitted from direct staff collaboration, but also the effectiveness of the outreach, demonstration and educational activities of the cooperative agreements has improved.

We do continue to utilize the traditional centers mechanism where it better serves the specific research objectives of the Institute. This is the case with the three centers that we currently support. These three centers comprise our Tropical Medicine Research Centers program, a component of our tropical diseases research portfolio. These foreign awards support research of direct relevance to the health of the people in tropical countries. In this case, we believe it is more appropriate for the host countries to manage the day-to-day affairs of these research programs. Thus we have elected to utilize the centers mechanism in this instance.

AIDS-HIV

Mr. Dickey: Although there is not yet a vaccine to prevent HIV infection, it seems we have discovered specific behaviors that can eliminate the spread of HIV, specifically the avoidance of unprotected sexual relations and intravenous drug abuse. If a man or woman is responsible enough not to become a member of one of these groups, what are his or her chances of becoming infected with HIV?

Dr. Fauci: The primary group of individuals that would not fall into one of these groups, would be newborns who are infected perinatally. In the United States, approximately 7,000 infants are born each year to HIV-infected women. One to two thousand of these infants are themselves HIV-infected. HIV is currently the fifth leading cause of death in children less than 15 years of age in the U.S.

That said, it is unrealistic to assume that most individuals at risk of HIV infection will remove themselves from risk-taking behaviors. Behavior change occurs only when one perceives risk and when one believes that an outcome can be affected by changing behavior or reducing risk.

Many individuals in the U.S. who are at risk of HIV infection still do not have access to the information regarding what constitutes risk or how to reduce it. Furthermore, sexual behaviors are among the most difficult to alter even when this information is available. Results from NIAID funded studies have shown that risk-taking groups do not abandon all risk-taking behavior even when repeatedly counselled regarding risk behaviors for HIV infection and how to reduce potential exposure to HIV.

In an effort to learn more about relevant behaviors within certain communities and develop better intervention strategies, the National Institute of Mental Health, the National Institute of Drug Abuse and the National Institute of Alcohol Abuse and Alcoholism support a range of biological, epidemiology, psychology and social research.

In other countries, such as Thailand and India, and throughout Africa, which are experiencing the greatest increase in AIDS, people do not generally have access to information that could lead to risk reduction, or in most cases, to affordable means of protecting themselves from HIV-infection. In many cultures, the specific behaviors required for protection from infection are socially unacceptable. For these reasons NIAID continues to invest in vaccine and other prevention research which we believe, in combination with behavioral intervention, will be the most effective and inexpensive means of preventing HIV disease and its spread, in the U.S. and throughout the world.

RESEARCH FUNDING LEVELS

Mr. Dickey: What criteria do you take into account when determining funding levels for the research of different diseases?

Dr. Fauci: We must take advantage of the windows of opportunity that become available in the evolution of a disease. This means funding research based on the scientific opportunities that the research presents. The funding of basic research is a high priority because it is aimed at discovering fundamental knowledge and can result in new knowledge that has applications to many diseases.

Mr. Dickey: Is any consideration given to the fact that some diseases, including lung cancer, and HIV/AIDS, can be virtually eliminated with moderate changes in behavior, while other diseases, including rheumatoid arthritis and some birth defects, apparently attack indiscriminately, regardless of behavior?

Dr. Fauci: There are a number of very serious health problems. You have named a few. There are more scientific opportunities than we have resources now for cancer, and the same can be said of heart disease and of other diseases. When looking at research funding, we must take advantage of the windows of opportunity that become available in the evolution of a disease. There is a time during the evolution of a disease when you can make a major impact.

This is where we are with HIV. While we are all sensitive to the importance of research in other areas, we feel as scientists and as people in the public health community that the funding level for HIV/AIDS is justified.

Mr. Dickey: Given limited resources, would you support prioritizing funds where the disease attacks an "innocent" person, rather that where the disease attacks a person who increased his or her risk to contracting the disease through behavioral choices?

Dr. Fauci: No, I would not. When looking at research funding, we must take advantage of the windows of opportunity that becomes available in the evolution of a disease. There is a time during the evolution of a disease when you can make a major impact.

Again, this is where we are with HIV. While we are all sensitive to the importance of research in other areas, and we are supporting these areas substantially within the constraints of our budgets, we must support those areas for which we can make the biggest impact. Basic research which is aimed at discovering fundamental knowledge, can result in new knowledge that has applications to many diseases. Research that for coding purposes is classified as cancer, heart or HIV/AIDS will increase the knowledge base used in our search for new or improved diagnostics, treatments, and vaccines for many diseases and not just for those for which the research is initially categorized.

AIDS-HIV

Mr. Stokes: AIDS has now become the leading cause of death for people 25 to 44 years of age. According to the Department, every three minutes one American dies of AIDS. What is the most significant research that is underway with respect to AIDS? Is AIDS a good candidate disease for the development of a vaccine or does gene therapy offer more hope for successful treatment than would the development of a vaccine? What is the FY 1996 investment in gene therapy for the restoration of immunity to HIV infection?

Dr. Fauci: NIAID has several significant research studies underway with respect to AIDS in the areas of basic research, therapeutics, epidemiology, and vaccines. NIAID's basic research efforts have generated an immense amount of information about HIV and continue to increase our understanding of the immunopathogenesis and multifactorial nature of the disease. NIAID investigators are examining how the virus causes damage and are now using newly developed, very precise assays to measure HIV in the body. With these assays, investigators are studying how and where HIV spreads in the bodies of patients with HIV disease, and are measuring the destruction of existing virus and the production of new immune system cells. This research may lead to new strategies for blocking or preventing viral damage.

NIAID basic research has revealed that therapeutic strategies for treating HIV disease must be multi-dimensional, addressing all of the disease's known pathogenic mechanisms. Building on this information, clinical trials are underway involving various drugs that are directed against multiple targets of the virus or the immune system. In addition, NIAID is conducting trials with combinations of drugs, which may prove to be more effective for treating HIV infected individuals as compared to single agents. Use of innovative therapeutic approaches also show promise. For example NIAID researchers have demonstrated that infusions of an immune system protein, interleukin-2 (IL-2) significantly boost the infection fighting white blood cells that are normally destroyed during HIV infection.

NIAID's epidemiological studies have increased our understanding of the disease, particularly in women who represent a growing proportion of people infected with HIV. NIAID's longitudinal cohort studies of long term non-progressors, individuals who have been infected with HIV for many years but show no sign of progression to clinical disease, and those who have been exposed to the virus but remain uninfected, are also essential to determining the immunological and virological factors that contribute to survival and potentially, protection from HIV-mediated disease. These studies are also elucidating specific factors that effect transmission, both maternal-fetal and sexual transmission of HIV.

NIAID's AIDS vaccine research efforts are moving candidate vaccines from the laboratory into animal and early human studies. Since 1988, more than 1,700 healthy, non-HIV infected adult volunteers have enrolled in 20 NIAID-supported clinical trials involving 14 vaccines. Research on HIV vaccine concepts is laying critical groundwork toward the eventual identification of a safe and effective vaccine that will provide protection against HIV-mediated disease and the transmission of HIV to others.

HIV is an excellent candidate for the development of a vaccine for use in non-HIV infected people. Ideally, a successful vaccine would prevent AIDS should vaccinated individuals be exposed to HIV after vaccination. A vaccine would be a powerful and valuable tool for preventing the spread of HIV in the U.S. and worldwide. With regard to therapeutic vaccines that would be used to boost the immune system of individuals already infected with HIV, studies are currently underway that will reveal the usefulness of such an approach.

Gene therapy offers hope for protecting individuals from the immune damage characteristic of AIDS and is currently in the early stages of clinical testing. NIAID funded investigators are also developing the first gene therapy strategy designed for HIV-infected children which has the potential for long-term gains.

In the President's FY 1996 budget, NIAID's investment in gene therapy to restore immunity in HIV infected individuals, including ribozyme research and the development of gene therapy approaches is $29.6 million.

Mr. Stokes: As the nation's war on cancer evolved, we learned that there was not just one cancer but hundreds of types of cancers. To what extent is AIDS following this pattern? Are we finding that there are numerous and varying strains of AIDS?

Dr. Fauci: Unlike cancer, which has multiple causes, all evidence to date points to HIV as the single etiologic agent that leads to AIDS. There are, however, numerous and varied strains of HIV and basic research is underway to further determine if the pathogenic potential of these strains vary. For example, in the SIV model, it is known that different strains of SIV have different, rather predictable courses of disease in monkeys. Research is underway to explore the extent to which the interplay of the different HIV strains with host characteristics leads to varying rates of HIV disease progression in humans.

Nonetheless, while there are different strains of HIV, all HIV strains share many of the same antiviral targets. Since all HIV strains do have common targets, the treatment of the primary HIV infection and approaches to block HIV replication are more likely to prove universal than blocking the replication of cancer cells. Exploring the potential significance of these different HIV strains to vaccine development is also an important and active area of research.

Mr. Stokes: The number of reports focusing on the life span of AIDS cells and the ability of the infected cells to spread the disease are increasing. What does this information really tell us about the characteristics of the disease?

Dr. Fauci: Measuring the quantity of virus present in HIV infected people and its relationship to the degree of immunity and disease progression, will be very important to evaluating therapeutic and prophylactic efforts against AIDS. NIAID funded researchers found that the persistent, low level viral replication found in the 5-10% of HIV-infected individuals referred to as long-term nonprogressors, is not necessarily associated with the progression of disease, if it is efficiently controlled over time. Also, NIAID sponsored studies have shown that if viral replication can be halted, immune cells are replenished. This suggests that if HIV replication is permanently stopped, the body will be able to regenerate immune cells. This information may lead to new strategies for treating HIV infection and for determining the effectiveness of new therapies for halting the spread of HIV in the body.

Mr. Stokes: AIDS continues to be an evolving disease and as we have learned more about the characteristics of this disease, its definition has changed to reflect the new knowledge we have gained. To what extent has the research focus changed?

Dr. Fauci: There are many stages of AIDS and by 1993, when the Centers for Disease Control and Prevention revised the definition of AIDS we had greater knowledge about the types of conditions that affect HIV infected people. The revision was made to more accurately reflect the status of individuals with compromised immune systems, and reflected the clinical importance of CD4+ lymphocyte count and included three other clinical conditions -- pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer. All of these changes, especially, invasive cervical cancer, were important to women, as well as other HIV infected people whose immune systems were severely compromised but had, until then, remained undiagnosed with, and unreported as, having AIDS.

The change in definition has not, however, affected the focus of NIAID's AIDS research efforts which have always encompassed the entire spectrum of the HIV disease and AIDS. NIAID has conducted and continues to support research on the prophylaxis and treatment on the opportunistic infections and malignancies associated with AIDS. Over the past few years, coinciding with the rise in Tuberculosis (TB) among people infected with HIV, NIAID has placed increased emphasis on TB, particularly in the area of prevention.

In 1991, even before the change in the definition of AIDS, NIAID initiated the Women's Interagency HIV Study (WIHS), a large long-term study that explores the natural history of HIV infection in U.S. women. The WIHS focuses on the spectrum and predictors of AIDS defining and other HIV-related conditions, including predictors of several diseases of the female reproductive system such as cervical neoplasia which leads to cervical cancer; markers and predictors of HIV disease progression related to the immune system, the virus, hormones and clinical symptoms; and trends in substance abuse, sexual behavior, health care utilization and social and economic factors.

AIDS IN MINORITY POPULATIONS

Mr. Stokes: Minorities continue to suffer disproportionately from AIDS. Currently, what AIDS research activities does your Institute support that are targeted to address AIDS in minority populations?

Dr. Fauci: One of the greatest challenges facing AIDS researchers today is the recruitment and retention of minority patients for clinical trials. People of minority background face unique social, economic, and medical problems in coping with the challenges attendant to HIV infection. As the epidemic expands in minority communities, inclusion of these patients in clinical trials is particularly urgent as it is important that the results of the research be applied to the populations greatly impacted by the disease.

The four major areas in which NIAID specifically addresses minority issues in HIV disease are treatment research, epidemiologic research, vaccine research, and infrastructure development and training of minority researchers.

In treatment research, NIAID in its extramural program directs a large national clinical trials program that consists of three components: the AIDS Clinical Trials Group (ACTG), the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), and the Division of AIDS Treatment Research Initiative (DATRI). All of these networks strive to ensure that a sufficient proportion of minority subjects are enrolled into the clinical trials so that the results of the research may be generalizable to the affected HIV population at large. NIAID works with these networks to identify the need for and/or assists in the development of culturally sensitive education materials and to identify real or potential barriers to recruitment and retention in clinical research for these groups and identify mechanisms to overcome these barriers. The current enrollment of people of minority background is 46% for the ACTG, 60% for the CPCRA, and 27% for DATRI.

In addition, NIAID developed the AIDS Clinical Trials in Minority Institutions RFA to encourage clinical HIV research performance at minority institutions. Four minority institutions, located at Howard University (Washington, D.C.), Meharry Medical College (Nashville, Tennessee), University of Puerto Rico (San Juan), and the University of Hawaii (Honolulu), received 4-year awards as adult AIDS Clinical Trials Units (ACTUs) in FY 1993. This program increased the number of minority staff members involved in ACTG research and the number of minority participants in clinical studies.

Three of these schools (Howard University, the University of Puerto Rico, and the University of Hawaii) were recipients of a 1990 NIAID initiative to improve the infrastructure of minority institutions, train minority biomedical researchers; and facilitate participation of these Institutions in NIAID's clinical trial agenda for AIDS.

In 1996, we will be recompeting the Adult ACTG. One of the criteria for this recompetition is to ensure the enrollment of a proportionate number of minorities at the sites. Additionally, within the OAR directed $60 million budget for the Adult ACTG, the NIAID has set aside $3.5 million exclusively for minority institutions.

In epidemiologic research, NIAID supports studies that explore the clinical, natural history, and transmission implications of HIV infection in a variety of populations. Groups of inner-city women, children, and drug users are the focus of the Heterosexual HIV Transmission Study (HATS) and the Women and Infants Transmission Study (WITS/WITSII). In addition, the Women's Interagency HIV Study (WIHS) is designed to describe the spectrum and course of clinical manifestations of HIV infection in women, particularly minorities. WIHS operates in tandem with the HIV Epidemiology Research Study (HERS), initiated in 1992 and sponsored by NIAID and CDC.

The Multicenter AIDS Cohort Study (MACS) and the San Francisco Men's Health Study (SFMHS) are prospective longitudinal studies of HIV disease in homosexual/bisexual men. In a second recruitment effort for MACS, minority populations were specifically targeted. In addition, the SFMHS is continuing to enroll a new cohort of young gay men, including those of minority background, into a substudy called the San Francisco Young Men's Health Study (SFYMHS). This study is following a cohort of young men who have grown up in a period of heightened public awareness of how the AIDS virus is transmitted and will provide invaluable information on how this has affected the risk-avoidance behavior of this population. Current enrollment of people of minority background in NIAID-supported epidemiology cohorts includes 17 percent for MACS, 63 percent for HATS, and 83 percent for WITS.

In the clinical component of vaccine research, NIAID directs the AIDS Vaccine Evaluation Units (AVEUs). The AVEUs are making an increased effort to enroll minorities in phase I and phase II clinical trials of candidate HIV vaccines. In collaboration with the NIH Office of Research on Minority Health, NIAID initiated in FY 1993 studies of factors influencing participation of minorities in HIV vaccine trials. In a recently initiated phase II trial, 25 percent of the volunteers were from minority populations.

NIAID now is working to prepare to conduct HIV vaccine efficacy trials. The current goals are to conduct epidemiologic and behavioral research on the incidence of HIV infection and cofactors for transmission in U.S. and international populations; conduct phase I and phase II studies of HIV vaccines in high-risk international populations; when appropriate, conduct large-scale efficacy trials of HIV vaccines in the United States and in international populations; and sponsor other high-priority intervention research studies.

NIAID supports baseline epidemiologic studies of HIV infection in injection drug users (IDUs) to determine if this would be an appropriate target population for vaccine efficacy trials. Of AIDS cases among IDUs, almost 80 percent occur among persons from minority groups. During FY 1994, the Division of Acquired Immunodeficiency

Syndrome (DAIDS) funded research, in collaboration with the National Institute on Drug Abuse, titled "Vaccine Preparedness Initiative", with the following specific objectives:

- to determine the incidence of HIV transmission in populations likely to participate in future vaccine efficacy trials, such as IDUs and individuals attending sexually transmitted disease clinics;
- to study the feasibility of conducting HIV vaccine trials in cohorts of IDUs;
- to evaluate the potential for recruitment and retention of these populations in future vaccine trials; and
- to identify special ethical, cultural, psychological, and social factors that are likely to enhance or discourage recruitment and` retention of these populations in future HIV vaccine efficacy trials.

NIAID staff members and investigators participated in the AIDS Action Foundation's Steering Committee on Social, Ethical, and Political Considerations for Domestic HIV Vaccine Efficacy Trials, which culminated in a public meeting May 9-10, 1994. This activity has initiated an important partnership among Government and academic scientists, industry, and representatives of communities at high risk for HIV infection in planning for vaccine efficacy trials.

Finally, NIAID has membership in both the Inclusion of Women and Minorities Committee, NIH, and the Program Subcommittee of the same umbrella committee. In this way, NIAID contributes to the development of policy and the tracking of NIH-sponsored studies for these populations.

NIAID worked with the AIDS Research Advisory Committee (ARAC) Task Force on the Recruitment and Retention of Underrepresented Populations into Clinical Trials. This ad hoc panel examined the issue of greater enrollment of underrepresented patient populations in clinical trials. A final report was presented at the March 1994 ARAC meeting.

TOPICAL MICROBICIDES

Mr. Stokes: Last year you emphasized the importance of the Institute's topical microbicides research effort and its implications for improving the treatment of infectious diseases. Doctor, what can you tell us this year that you could not tell us last year about progress in this area?

Dr. Fauci: We have moved forward in basic research, product development and clinical evaluation efforts.

BASIC RESEARCH:

In 1994 the NIAID issued a request for applications (RFA) for program projects for basic research leading to the development of topical microbicides. The purpose of the RFA was to expand research in this area through the conduct of multi-disciplinary research in microbiology, immunology, reproductive biology, reproductive toxicology, and cell biology. Basic and applied research leading to effective strategies for intravaginal protection against STDs, including HIV infection, was encouraged. The NIAID awarded three program projects to the Children's Hospital in Cincinnati, the University of California Los Angeles, and the University of Pittsburgh. In addition to relevant basic research, the program projects include four new and innovative approaches to the prevention of STDs through chemical barrier methods. Research on topical microbicides was also encouraged in the recompetition of the STD Cooperative Research Centers. Topical microbicide research has been proposed in several of the applications submitted.

PRODUCT DEVELOPMENT:

NIAID staff have been pro-active in contacting commercial representatives about new and existing products in various stages of development. In the last year over a dozen companies have expressed interest in collaborating on some aspect of product development and/or evaluation. We are working to provide guidance and assistance in pre-clinical and clinical testing. Commercial collaborators are involved in two of the three recently awarded topical microbicide program projects. Finally NIAID is working with the FDA to clarify relevant regulatory requirements. This will be of great value as we move forward with commercial partners to evaluate topical microbicides in clinical trials.

ClINICAL EVALUATION:

In order to determine what conclusions might be drawn from previous studies using spermicides to prevent STDs and HIV infection, NIAID staff have just completed a comprehensive review of the literature. A review paper will be published in the summer of 1995. Based on this review, there have been no well designed clinical trials to answer this question, consequently no recommendation can be made about safety or efficacy. It should be noted that there have been studies in which a trend toward protection from bacterial STDs is apparent.

Currently, the NIAID is sponsoring a randomized double blind clinical trial in the Cameroon to evaluate the safety and efficacy of VCF, a vaginal contraceptive film that contains 72 mg of N-9 spermicide. Results from this study will be monitored by a data safety and monitoring board. It is scheduled to be completed in 1998.

RESEARCH PROJECT GRANTS

Mr. Stokes: Currently, what is the total number of research project grants funded by your institute? How does this compare to the number funded in FY 1994 and the proposed number for FY 1996? What is the success rate for each of these years? For the NIH as a whole, the number of research project grants awarded appears to be remaining fairly constant, is this trend true for your institute as well?

Dr. Fauci: The following table identifies NIAID's number of research project grants and success rate for Fiscal Years 1994 through 1996:

	FY 1994	FY 1995	FY 1996
Number of Research Project Grants Funded	2,525	2,557	2,569
Success Rate	24.5%	25.4%	27.6%

Mr. Stokes: If we look at five year increments, what has happened to your Institute's success rate over the past five to ten to fifteen years. Explain.

Dr. Fauci: In FY 1982, the NIAID success rate was 28.6 percent. Due to large increases in funding for AIDS research in the mid-1980's, the success rate increased to 37 percent in FY 1983 and remained relatively constant until FY 1990 when it decreased to 28 percent. From FY 1990 until FY 1994 the success rate remained constant at about 29 percent. In FY 1994 the success rate dropped to 24.5 percent due to a decrease in our Non-AIDS appropriation. The NIAID success rate is expected to increase to 25.4 percent in FY 1995 and 27.6 percent in FY 1996.

RESEARCH PROJECT GRANTS AWARDED TO MINORITY INSTITUTIONS & RESEARCHERS

Mr. Stokes: What is the success rate for research applications received from African American researchers? From Historically Black Colleges and Universities?

Dr. Fauci: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. The NIAID is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Because a significant number of grant applicants choose not to complete the portion of the grant application referring to race and gender, success rate data are statistically invalid. For instance, in FY 1994, 33 percent of NIAID applicants chose not to answer the optional questions, making it impossible to draw any conclusions about success rates in racial categories in FY 1994. Our success rate for Historically Black Colleges and Universities was 8.3 percent in FY 1994.

Mr. Stokes: What has been the trend in the average cost of the Institute's research project grants in general over that same time period? What does the trend look like in terms of constant dollars? What is the average costs of research project grants awarded to women? To minority researchers? To African American researchers? To Historically Black Colleges and Universities?

Dr. Fauci: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. The NIAID is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Because a significant number of grant applicants choose not to complete the portion of the grant application referring to race and gender, it is statistically invalid and impossible to give an average cost by gender or race. However, the following table displays the average costs of NIAID Research Project Grants in general and the Historically Black Colleges and Universities:

NIAID Average Costs
(dollars in thousands)

	FY 1985		FY 1989		FY 1994	
	Current	CPI	Current	CPI	Current	CPI
RPGs	$143	$143	$216	$187	$263	$189
HBCUs	163	163	134	117	380	273

Mr. Stokes: According to a November 1993 article appearing in the chronicle of higher education, white scholars received 90 percent of the research grants awarded to competitively by the National Institutes of Health in 1991, according to a study by the agency. The study found that in the same fiscal year, Asians had received about 8 percent of such grants, Hispanics 1.5 percent, African Americans 0.4 percent. What are the current statistics for your Institute?

Dr. Fauci: To comply with federal mandates, all questions related to race are identified as optional on all NIH research grant applications. The NIAID is unable to identify accurately the number of applications submitted by minorities or the number of awards to minorities. Because a significant number of grant applicants choose not to complete the portion of the grant application referring to race, such data are statistically invalid. For instance, in FY 1994, 33 percent of NIAID applicants chose not to answer the optional questions, making it impossible to draw any conclusions about racial categories in FY 1994.

PARTICIPATION OF MINORITIES AND WOMEN IN CLINICAL TRIALS

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health indicated, in testimony before the Committee this year, that the Department is enhancing its efforts to close the health disparity gap. You may recall that last year, when I asked you to respond to the statement that the "the minority health crisis continues, whiles we continue to witness an unprecedented explosion of scientific knowledge; while we have a phenomenal capacity to treat and cure disease; and while medical breakthroughs are affording Americans a longer life expectancy." At that time you indicated that is an accurate statement and that the system is such that minorities find themselves unable to benefit from advances in biomedical research, and even unable to participate in clinical research trials. Doctor, how much progress have we made since you were here last?

Dr. Fauci: We continue to stress to our extramural and intramural research scientists that their clinical trial efforts must be reflective of disease occurrence among the U.S. population of this country. With the study of AIDS, we have had much success in matching or exceeding the incidence rate of the disease in the general population in our clinical trials. The Institute recently initiated a Tuberculosis clinical study which involves the collaboration of NIAID researchers and the staffs of minority clinics and medical institutions in Washington, D.C.

On October 1, 1994, new NIH Clinical Research Guidelines made mandatory what we have required our AIDS grantees and researchers to do in this area. The new guidelines make it a requirement that all clinical trials must make every attempt to include minorities and women in their clinical studies. NIAID intends to continue to require that our extramural and intramural researchers make every effort to recruit women and minorities to its trials.

ASTHMA

Mr. Stokes: Asthma continues to be a major medical problem affecting 10 million Americans, more than one-third of whom are under 18 years of age. Last year, you indicated that recent studies reveal that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. Are we making any measurable progress in this research area and what can you tell us this year that you could not tell us last year about this disease?

Dr. Fauci: Preliminary analyses from 1,528 children (73% African American and 20% Latino) who participated in the initial phase of the NIAID Inner City Asthma Study have been completed. During a course of a 12 month followup these children experienced an average of 3.4 visits to the emergency room and 0.6 hospitalizations, confirming our impression that they experienced increased morbidity. In addition we have demonstrated a high level of cockroach allergen levels in their home environment and that allergy to the cockroach appears to play an important part in their illness. Finally asthma self-management skills are lacking among the asthmatics and their families.

Based on these findings, we launched the second phase of this study in November, 1994 and have already enrolled over 960 children and their families into an intervention program which incorporates efforts at eradication of cockroaches combined with improved coordination of asthma treatment. Results are expected in 1996. It is anticipated that this intervention will result in fewer hospitalizations and visits to emergency rooms as well as less days with asthma symptoms.

Mr. Stokes: How much is included in the FY 1996 budget for this trial?

Dr. Fauci: Future plans, which include the continuation of the National Cooperative Inner-City Asthma Study as well as demonstration and education projects within the Asthma Centers program and individual research grants, will enable the NIAID to assess the effectiveness of specific interventions, make necessary improvements/refinements, and apply these culturally appropriate approaches to additional geographic locations and minority populations with asthma. The NIAID will continue funding of the inner-city asthma studies in FY 1996 estimated at $3.4 million and we will increase our overall asthma funding from $13 million in FY 1995 to $13.3 million in FY 1996.

KIDNEY TRANSPLANTATION

Mr. Stokes: Are we making significant progress with respect to organ and tissue transplantation? To what extent have we made improvement in curtailing organ and tissue rejection? I understand that minorities, especially Native and African Americans require kidney transplants more often than their white counterparts. To what is this attributed and to what extent is the institute addressing this problem?

Dr. Fauci: The success of organ and tissue transplantation depends on many factors, including the health of the recipient at the time of transplantation and the histocompatibility matching between the donor organ and the recipient. New techniques in histocompatibility matching and new immunosuppressive drugs have greatly helped to ensure that an engrafted organ is not rejected early after transplantation. However, the new drugs have not had a significant impact on long term graft survival. NIAID is currently supporting both clinical research and clinical trials focused on increasing long term kidney graft survival. These efforts emphasize using the immune system itself to prevent the rejection from occurring rather than trying to rely on drugs to stop the rejection once it has occurred. NIAID is currently supporting two clinical trials, one in adults and one in children to try and decrease the incidence of kidney graft failure and subsequent retransplantation.

African-Americans have four times the rate of End Stage Renal Disease as Caucasians. Native Americans have about six times the rate of kidney failure as Caucasians, primarily due to complications associated with diabetes. NIAID supports research aimed at understanding the immunopathogenesis and the genetics of diabetes. NIAID has long standing efforts aimed at improving histocompatibility typing. This effort was expanded over seven years ago to increase the knowledge about the histocompatibility types in African-Americans with the end result being the full definition of the histocompatibility types and subsequent improved access to transplantation. This same histocompatibility matching effort has been extended to Native Americans and Hispanics.

In addition, African-Americans are transplanted less frequently due to a high reactivity to histocompatibility antigens, a so called "positive cross match". If someone is transplanted with an organ to which they have a "positive cross match", the organ is rejected very quickly and vigorously, usually resulting in loss of the organ. NIAID clinical trials are investigating a new way to reduce this "positive cross match" and not only allow African-Americans to be transplanted more frequently, but with a higher degree of success.

VACCINE INITIATIVE

Mr. Stokes: To what extent will the FY 1996 budget allow the Institute to advance its vaccine research initiative? Which diseases are prime candidates for the development of vaccines?

Dr. Fauci: Vaccines represent the most cost-effective method to prevent a range of infectious diseases that affect all age groups. NIAID's vaccine activities cover the entire research spectrum: basic discoveries, preclinical development, early clinical studies, and appropriately scaled and controlled efficacy trials. Several special vaccine activities for FY 1996 are accommodated within the existing budget. These include: 1) research needed to develop vaccines to prevent pneumonia, diarrhea, liver disease, and gastric ulcers, 2) maternal immunization studies aimed at protecting newborns against streptococcal disease, and 3) vaccine production.

NIAID encourages investigator-initiated research project grants on important human pathogens. Research on pathogenesis and the immune response are particularly crucial for vaccine development. New findings lead these investigators to develop early stage vaccine candidates and evaluate them in animal models. To the extent that its budget allows, NIAID will fund this basic and developmental research.

NIAID has established a small but vital infrastructure to assist both academic and small business investigators in translating their research into benefits for public health. First, NIAID has established capability to scale-up, produce, and safety-test a variety of vaccines. One example is investigators who developed three different, viable vaccine candidates for prevention of childhood rotavirus diarrhea. NIAID has produced two of these and the third is under production.

Second, since these vaccine candidates are made under Good Manufacturing Practices, they can progress to the next infrastructure stage -- clinical evaluation at NIAID's Vaccine and Treatment Evaluation Units. An example was the use of this capability to demonstrate one of the rotavirus candidate vaccine's efficacy in protecting infants from diarrhea. NIAID's assistance helped the transfer of the two produced candidates to corporate groups for further development and testing.

Vaccination strategies for preventing infection and disease are likely to be highly effective and cost-beneficial for many diseases. Diseases that are prime candidates for developing vaccines include:

- respiratory infections manifesting as pneumonia, meningitis, and pharyngitis and caused by various fungal, bacterial and viral organisms;
- enteric diseases such as diarrhea and food poisoning, gastric ulcers (Helicobacter pylori), bloody diarrhea and hemolytic uremic syndrome (enterohemoraghic E. coli);
- chronic liver disease caused by hepatitis C;

-- sexually transmitted diseases such as gonorrhea, chlamydia, and herpes infections; and

-- re-emerging infections such as malaria, dengue, tuberculosis, and group A streptococci.

CLINICAL TRIALS

Mr. Stokes: Clinical trials appear to be the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits to the American people and has yielded comparable economic savings. What level of funding is included in your institute's FY 1996 budget request for clinical trials? How many trials would be funded? How many of these trials are new and how many are ongoing?

Dr. Fauci: The NIAID will devote approximately $265,479,000 to it's Clinical Trial program. This level of funding will support many major clinical trials such as the AIDS Clinical Trial Group, the Terry Beirn Community Program for Clinical Research on AIDS, the National Cooperative Inner-City Asthma Studies and several other supporting clinical research efforts. In FY 1996 all of these trials are ongoing.

Mr. Stokes: Is there a specific system in place at your Institute for disseminating important information stemming from the results of clinical trials?

Dr. Fauci: The results of NIAID-supported clinical trials are disseminated to researchers, health care professionals, patients and the general public in a number of ways. Study results are reported in peer-reviewed medical journals that are widely read by health professionals, made available on online databases, discussed at scientific meetings, and disseminated to the press and the public through press releases and, when appropriate, press conferences. In cases in which significant findings may impact on the treatment of persons with diseases that threaten their lives or vital organs, NIAID follows the 1991 recommendations of an NIAID ad hoc Blue Ribbon Committee on Early Dissemination of Research Results. Immediately following the conclusion of a study or recommendations from the Data and Safety Monitoring Board to terminate or change a study, NIAID notifies the public. This is generally accomplished through the media and announcements to physicians organizations and constituent groups. Shortly thereafter, NIAID convenes a group of experts to analyze the data to determine whether early dissemination is warranted and, if so, to prepare a summary. The summary is issued as a Clinical Alert to physicians and contains enough information to enable practicing physicians to make interim treatment decisions on a case-by-case basis. Clinical Alerts are distributed through the National Library of Medicine mechanisms, mailings to physicians, media alerts, physician organizations, and other channels. NIAID's system structure follows guidelines set by NIH, and published in the Journal of the American Medical Association in June 1993 for early dissemination of results from clinical trials.

Mr. Stokes: What progress is being made in increasing the numbers of women and minorities in clinical trials?

Dr. Fauci: We are actively engaged in exploring how to attract women and minorities to our studies and have an extensive outreach program to encourage minorities to participate in our clinical studies. NIAID and the AIDS Clinical Trials Information Service provided exhibits and/or materials for many national and regional meetings focusing on concerns of minority populations, including the 10th Biennial National Conference on Hispanic Health and Human Services; conferences sponsored by La Raza, Blacks in Government, the National Association of Community Health Centers, the National Minority AIDS Council, and the Congressional Black Caucus/Health Braintrust; and several meetings in Puerto Rico sponsored by the Health Resources and Services Administration, among others.

The inclusion of women in our AIDS clinical trials has increased steadily since 1988. Currently, women represent over 14 percent of the patients on study in AIDS therapeutic clinical trials. The current percentage of women on study in the ACTG is 11 percent; the CPCRA is 20 percent and DATRI is 18 percent. Women make up 50 percent of the patients currently on study for the AIDS Evaluation Group. This trend is reflective of the history of the epidemic in women which began expanding in women in the mid-1980's. The current enrollment of people of minority background in NIAID-supported therapeutic clinical trials 46 percent for the ACTG, 60 percent for the CPCRA, and 27 percent for the DATRI.

In addition, NIAID developed the AIDS Clinical Trials in Minority Institutions RFA to encourage clinical HIV research performance at minority institutions. Four minority institutions, located at Howard University (Washington, D.C.), Meharry Medical College (Nashville, Tennessee), University of Puerto Rico (San Juan), and the University of Hawaii (Honolulu), received 4-year awards as adult AIDS Clinical Trials Units (ACTUs) in FY 1993. This program increased the number of minority staff members involved in ACTG research and the number of minority participants in clinical studies.

In 1996, we will be recompeting the Adult ACTG. One of the criteria for this recompetition is to ensure the enrollemnt of a proportionate number of minorities at the sites. Additionally, within the OAR directed $60 million budget for the Adult ACTG, the NIAID has set aside $3.5 million exclusively for minority institutions.

Several initiatives have been designed to more clearly define HIV disease in women through epidemiologic research so that researchers can design clinical trials to address research questions of greatest therapeutic relevance to women. In 1993, the PHS multi-agency sponsored Women's Interagency HIV Study (WIHS), of which NIAID is a sponsor, was initiated. It is a collaborative, multi-site, longitudinal study designed to investigate the impact of HIV infection on women. The study population, once enrollment is complete, will include approximately 2,000 HIV-infected women and 500 HIV-uninfected females at high risk of acquiring HIV who are aged 13 years or older at the time of enrollment.

The NIAID-sponsored Women and Infants Transmission Study (WITS I/II) examines factors related to HIV transmission during pregnancy or birth as well as the progression of the disease in women during pregnancy. WITS is being conducted in five cities: Chicago, Boston, Puerto Rico, New York City and Houston.

Our 5 year Urban Asthma Study is targeted to minority children suffering from asthma and residing in urban centers. Data collection for phase I of the National Cooperative Inner-City Asthma Study (NCICAS) was completed in 1994. This ongoing multicenter study explores the factors that contribute to the increasing rates of morbidity and mortality among inner-city African American and Hispanic/Latino children. Phase I resulted in the development of culturally appropriate questionnaires to measure asthma morbidity and compliance with asthma therapy, procedures to measure allergen levels, and a coding scheme to evaluate doctor-patient communication.

Phase II of NCICAS has begun and includes interventions to reduce allergen levels, assignment of asthma counselors to inner-city families to empower them to make better use of the medical care system, facilitation of asthma treatment and access to care, and education of patients on self-management skills.

In FY 1991, the NIAID launched the first NIH cooperative clinical trial in kidney transplantation, a multicenter prospective study designed to translate some of the most recent developments of basic research into new immunosuppressive modalities to prevent kidney graft rejection. A network of transplantation centers throughout the United States is evaluating new immunosuppressive agents as they become available. Efforts were made and have been successful at recruiting women for this trial. Women, as a result of them bearing children, develop antibodies directed against the human leukocyte antigens inherited from the father, which in turn, reduces their chances for compatibility with an organ donor. While these antibodies can be present due to other causes, e.g., transfusions, and can be present in men, high titers of these antibodies occur more frequently in women.

FULL TIME EQUIVALENT (FTE) FREEZE

Mr. Stokes: Is the institute currently under an FTE freeze and if so, how long has it been under this freeze, and how is it impacting operations.

Dr. Fauci: The NIAID is not currently under an FTE freeze. However, we are operating under a freeze on senior level positions at the GS-14 and above level. The Administration's policy is that ten percent of our FTE reduction come from GS-14, GS-15 and SES level positions. The Department has sought a waiver to exempt senior level staff from this reduction in those cases where the grade level is based on expertise, not managerial or supervisory criteria. Until such a waiver is approved, this freeze is impacting upon our ability to hire and retain the very best young scientists with whom we have invested many years and substantial resources. Additionally, we cannot hire senior level scientists within our extramural research divisions. This affects our ability to evaluate research applications, resulting in deferrals and delays in making extramural grant and contract awards. Eventually this may affect our ability to rapidly respond to changes in scientific direction. Finally, the freeze on these senior level positions is hampering our ability to move women and minorities into upper level management positions within the institute.

RE-EMERGING DISEASES

Mr. Stokes: The re-emergence of infectious diseases is causing tremendous national concern. What are the most significant diseases that fall into this category, and what research is underway to address them?

Dr. Fauci: Recent media attention has highlighted the potential for emerging viral diseases, but in fact the possibility also exists for many bacterial, fungal or parasitic infections to emerge or re-emerge in the U.S. The 1992 Institute of Medicine report on *Emerging Infections: Microbial Threats to Health in the United States* presented a lengthy list of emergent diseases in each of these categories. Moreover, we are all aware of recent examples such as unexpected outbreaks of hantavirus infection in the Southwest, Lyme Disease in the Northeast, coccidioidomycosis in California and cryptosporidiosis in Wisconsin. Increases in population density, urbanization, and worldwide commerce and travel, as well as environmental changes, all contribute to the prospects for emergence or re-emergence of infectious diseases. In addition, indiscriminant use of antimicrobials has led to the development of drug resistance by some pathogens that were once thought to be controllable, such as tuberculosis and malaria.

NIAID has made a concerted effort to address emerging disease threats as they appear, for example by greatly expanding research efforts on diseases such as AIDS, Lyme and tuberculosis. The exact nature of any future emerging disease threat may be difficult to predict, however. To successfully confront this challenge requires critical knowledge of the fundamental biology of infectious agents and the clinical disease processes they induce. For that reason, NIAID supports a broad and comprehensive program of fundamental research, research training and applied research to strengthen national surveillance and response capabilities. Topics related to emerging diseases include research on: 1) fundamental aspects of microbial physiology, genetics and biochemistry that will elucidate the mechanisms of antibiotic resistance and facilitate identification of new intervention strategies; 2) pathogenesis of viral, bacterial, fungal and parasitic diseases; 3) host immune responses to infection; 4) the development of new interventions, including vaccines, therapeutics and diagnostic tests; and, 5) transmission dynamics of infectious diseases, including studies of vector biology and environmental influences. Since it is clear that the issue of emerging diseases is global in scope and cannot be addressed by our country in isolation, the NIAID also maintains strong international ties through programs such as the International Collaborations in Infectious Diseases Research.

Mr. Stokes: In your professional judgement, what type of national strategy is needed and would be effective in addressing this national problem?

Dr. Fauci: The problem presented by the threat of emerging infectious diseases requires that our country maintain its international leadership role in basic biomedical and epidemiologic research. Laboratory and epidemiologic research are the essential twin foundations upon which sound surveillance and appropriate response are based, and this is especially true in regard to emerging infections. Epidemiologic research into transmission patterns and risk factors provide the critical link between a disease and its causative agent that allows an effective public health response. No effective control measure may yet be available, however, for newly emerging diseases or for those that are re-emerging due to the development of resistance to previous control methods. Our ability to address such threats adequately will in large part depend on the success of basic biomedical research. Research to improve fundamental understanding of the processes of microbial evolution, the genetic basis for virulence, and the immune mechanisms involved in resistance and disease lays the groundwork for development of new or improved diagnostic and therapeutic strategies, vaccines, and methods to prevent the transmission of infectious agents. Efforts to protect our country from emerging disease threats will also require sustained support for international research and training. It is intuitively obvious that an improved capacity to detect and contain infectious disease threats where they originate, before they spread internationally, will benefit the U.S. With ever increasing international travel and commerce, this country can not afford a "fortress mentality". Importation of new microbes can occur with every international air flight, and every shipment of food or other goods. Support for the further development of strong public health capabilities abroad, particularly in tropical and other developing regions where infectious diseases often tend to first emerge, is a national security issue. Long-term, sustainable, support for collaborative international laboratory and epidemiologic research and research training programs provides an important opportunity to achieve this goal.

Mr. Stokes: What is the status of the rapid diagnostic test for tuberculosis?

Dr. Fauci: There are two new tests that can be used for the rapid diagnosis of tuberculosis.

1) PCR (polymerase chain reaction) for the early detection of M. tb in clinical samples is a test system that is under active development by three manufactures Hoffman La Roche, GeneProbe and Becton & Dickenson. Although some problems remain, regarding the sensitivity and specificity of these diagnostic kits, it is anticipated that the technology exists to overcome these problems.

2) The Luciferase assay for drug susceptibility test shows great promise. Although still under development, most of the technical problems have been resolved. Under an NIAID contract to Case Western Reserve University, the test system is currently being evaluated at Monteifore Hospital Medical Center in New York City. Preliminary data has shown the specificity to be excellent. Efforts are now directed to improving the sensitivity of the test.

The luciferase has been licensed to Becton & Dickenson for product development, although this company has recently decided not to pursue this opportunity.

TOPICAL MICROBICIDES

Ms. Lowey: What specific efforts are being made in basic research to support the development of new products?

Dr. Fauci: In 1994 the NIAID issued a request for applications (RFA) for program projects for basic research leading to the development of topical microbicides. The purpose of the RFA was to expand research in this area through the conduct of multidisciplinary research in microbiology, immunology, reproductive biology, reproductive toxicology, and cell biology. Basic and applied research leading to effective strategies for intravaginal protection against STDs, including HIV infection, was encouraged. The NIAID awarded three program projects to the Children's Hospital in Cincinnati, the University of California Los Angeles, and the University of Pittsburgh. In addition to relevant basic research, the program projects include four new and innovative approaches to prevention of STDs through chemical barrier methods. Research on topical microbicides was also encouraged in the recompetition of the STD Cooperative Research Centers. Topical microbicide research has been proposed in several of the applications submitted.

Ms. Lowey: Could you explain how the Institute is working with the commercial sector to facilitate the development and evaluation of new products?

Dr. Fauci: NIAID staff have been pro-active in contacting commercial representatives about new and existing products in various stages of development. In the last year over a dozen companies have expressed interest in collaborating on some aspect of product development and/or evaluation. We are working to provide guidance and assistance in pre-clinical and clinical testing. Commercial collaborators are involved in two of the three recently awarded topical microbicide program projects. Finally NIAID is working with the FDA to clarify relevant regulatory requirements. This will be of great value as we move forward with commercial partners to evaluate topical microbicides in clinical trials.

Ms. Lowey: What efforts are being made to determine whether or not existing products can be used safely and effectively as microbicides? What clinical studies are in progress or are planned to assess use of N-9 containing spermicides or lubricants for prevention of HIV and other sexually transmitted diseases?

Dr. Fauci: In order to determine what conclusions might be drawn from previous studies using spermicides to prevent STDs and HIV infection, NIAID staff have just completed a comprehensive review of the literature. A review paper will be published in the summer of 1995. Based on this review, there have been no well designed clinical trials to answer this question, consequently no recommendation can be made about safety or efficacy. It should be noted that there have been studies in which a trend toward protection from bacterial STDs is apparent.

Currently, the NIAID is sponsoring a randomized double blind clinical trial in the Cameroon to evaluate the safety and efficacy of VCF, a vaginal contraceptive film that contains 72 mg of N-9 spermicide. Results from this study will be monitored by a data safety and monitoring board. This study is scheduled to be completed in 1998.

Ms. Lowey: How will men benefit from the use of female controlled barrier methods like topical microbicides?

Dr. Fauci: Chemical barriers that inactivate pathogens in vaginal/cervical secretions as well as in the ejaculate will reduce female-to-male as well as male-to-female transmission. Furthermore, prevention of pregnancy and prevention of infection are both extremely important to women and to men. Development of chemical barriers that do both safely and effectively are needed. Finally, a non-contraceptive method designed to prevent infection is needed also by both men and women for several reasons: 1) the lack of barrier methods for disease prevention that permits conception (consequently procreation has become life threatening); 2) the constant requirement to prevent infection throughout reproductive life, regardless of contraceptive choice or need; 3) the use of several contraceptive methods that have either no effect on or increase risk of STD transmission; and 4) the need to prevent STDs during non-reproductive years.

Ms. Lowey: What resources would be required to continue or expedite the progress you are making in this area? Given we do not expect any major increase in funds for this effort, how will you sustain the rate of progress?

Dr. Fauci: Development of safe effective topical microbicides is undoubtedly a long term, expensive effort. That said, within the current and predicted budget constraints, topical microbicides will continue to be a high priority for the institute. NIAID is assessing existing capabilities for pre-clinical and clinical evaluation of drugs and vaccines with the aim of increasing the capacity of this infrastructure to include evaluation of topical microbicides. Close collaboration with other NIH institutes, PHS agencies as well as domestic and international non-governmental agencies, will enable us to pool our resources and to facilitate rapid development and evaluation of these products. For example, use of international clinical trials infrastructure is a cost effective way to evaluate topical microbicides while providing an opportunity to assess feasibility of these products to prevent and control STDs/HIV in the developing world.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

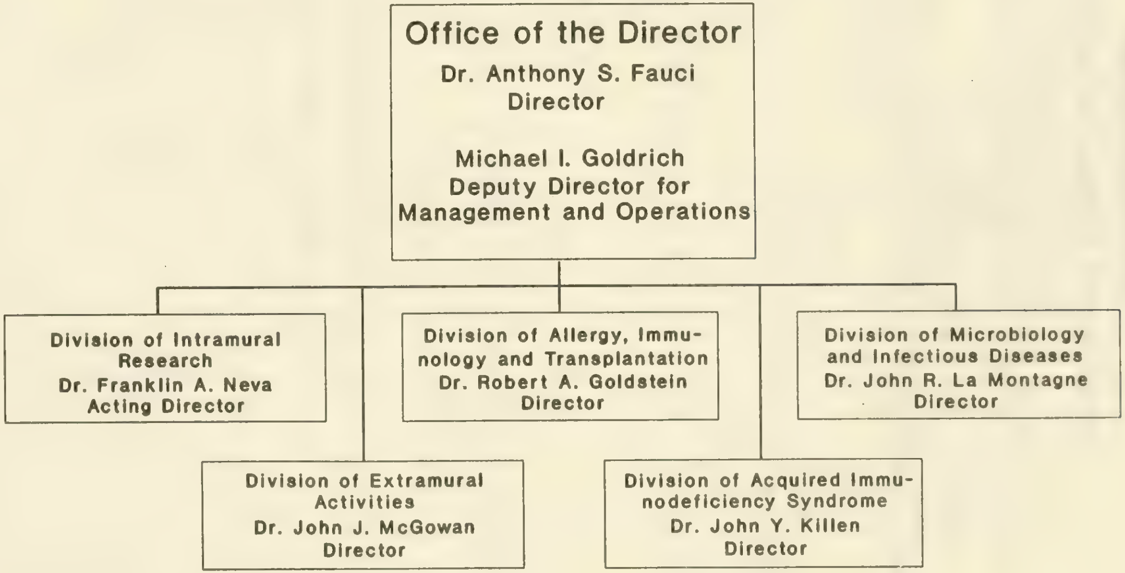
National Institute of Allergy and Infectious Diseases

FY 1996 Budget	Page No.
Organization chart	88
Appropriation language	89
Amounts available for obligation	91
Budget mechanism table	92
Summary of changes	94
Budget authority by object	96
Administrative costs	98
Significant items in House and Senate Appropriations Committee Reports	99
Authorizing legislation	104
Appropriation history	105
Budget authority by activity	107
Justification:	
A. General statement	109
B. Extramural research	111
C. Intramural research	117
D. Research management and support	120
E. Detail of full-time equivalent employment (FTE)	122
F. Detail of end-of-year employment	123

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Organization Structure



Office of the Director
Dr. Anthony S. Fauci
Director

Michael I. Goldrich
Deputy Director for
Management and Operations

Division of Intramural Research
Dr. Franklin A. Neva
Acting Director

Division of Allergy, Immunology and Transplantation
Dr. Robert A. Goldstein
Director

Division of Microbiology and Infectious Diseases
Dr. John R. La Montagne
Director

Division of Extramural Activities
Dr. John J. McGowan
Director

Division of Acquired Immunodeficiency Syndrome
Dr. John Y. Killen
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [536,416,000] *$557,354,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995. P.L. 103-333.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$1,065,583,000	$536,416,000	$557,354,000
Section 205 procurement reduction......................		-308,000	
Section 207 rent reduction........		-4,000	
Section 513 S&E reduction.........		-257,000	
Enacted rescission in accordance with PL 103-211................	-1,879,000		
Subtotal, Adjusted appropriation................	1,063,704,000	535,847,000	557,354,000
Comparative transfer to:			
NIH Office of AIDS Research for HIV research activities.......	-542,912,000		
Comparative transfer from:			
Other NIH institutes for management fund billing adjustment..................	2,065,000	2,199,000	
Subtotal, adjusted budget authority............	522,857,000	538,046,000	557,354,000
Unobligated balance, lapsing......	-8,000	---	---
Total obligations..............	522,849,000	538,046,000	557,354,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1994 - $21,425,000; 1995 - $24,000,000; 1996 - $29,000,000

Excludes funding for HIV research Activities: 1995 - 558,411,000; 1996 - $596,018,000

Note: Excludes $4,680,000 for royalties received in 1994 and $5,000,000 in 1995.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases
Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	1,211	$264,576,000	1,235	$275,970,000	1,176	$268,232,000
Admin. supplemental	(42)	1,362,000	(42)	1,389,000	(42)	1,417,000
Competing						
Renewal	149	34,106,000	140	33,433,000	172	42,732,000
New	228	43,409,000	214	42,331,000	262	54,054,000
Supplemental	1	142,000	1	148,000	1	154,000
Subtotal, competing	378	77,657,000	355	75,912,000	435	96,940,000
Subtotal	1,589	343,595,000	1,590	353,271,000	1,611	366,589,000
SBIR/STTR	58	7,647,000	65	8,870,000	66	9,342,000
Subtotal, research projects	1,647	351,242,000	1,655	362,141,000	1,677	375,931,000
Research centers						
Specialized/comprehensive	3	1,227,000	3	1,264,000	3	1,307,000
Research Centers in Minority Institutions						
Subtotal, research centers	3	1,227,000	3	1,264,000	3	1,307,000
Other research						
Research career program	113	8,533,000	113	8,789,000	114	9,096,000
Minority biomedical support	--	692,000	--	713,000	--	738,000
Other	16	625,000	16	645,000	16	668,000
Subtotal, other research	129	9,850,000	129	10,147,000	130	10,502,000
Total, research grants	1,779	362,319,000	1,787	373,552,000	1,810	387,740,000

Training						
Individual awards						
Noncompeting..............	43	1,207,000	37	1,069,000	44	1,302,000
Competing, new............	41	1,107,000	47	1,314,000	41	1,164,000
Subtotal, individual....	84	2,314,000	84	2,383,000	85	2,466,000
Institutional Awards						
Noncompeting..............	478	12,770,000	487	13,376,000	489	13,821,000
Competing						
Renewal.................	52	1,090,000	45	971,000	46	1,030,000
New.....................	13	398,000	11	339,000	11	349,000
Subtotal, institutional	543	14,258,000	543	14,686,000	546	15,200,000
Total, training............	627	16,572,000	627	17,069,000	631	17,666,000
R&D Contracts.................	67	43,872,000	67	45,180,000	67	46,780,000
(SBIR/STTR)	(5)	(352,000)				
	FTEs		FTEs		FTEs	
Intramural research...........	636	75,750,000	641	77,481,000	634	79,704,000
Research management and support....................	466	24,344,000	466	24,764,000	462	25,464,000
	1,102	522,857,000	1,107	538,046,000	1,096	557,354,000
Clinical Trials...............		(50,209,000)		(51,665,000)		(52,699,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes

1995 Estimated budget authority	$538,046,000
1996 Estimated budget authority	557,354,000
Net change	+19,308,000

	1995 Current Estimate Base		Change from Base	
	(FTEs)	Budget Authority	(FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Intramural				
a. Within grade increase		$ 32,782,000		+$453,000
b. One more day of pay		32,782,000		+126,000
c. Annualization of FY 1995 pay raise		32,782,000		+269,000
d. January 1996 pay raise		32,782,000		+554,000
e. FECF increase		32,782,000		+3,000
f. Payment for centrally furnished services		15,964,000		+474,000
g. Service and supply fund increase		3,276,000		+134,000
h. Increased cost of laboratory materials and supplies		25,351,000		+766,000
i. FTS 2000 reduction		108,000		-24,000
Subtotal				+2,755,000
2. Research Management and Support				
a. Within grade increase		14,699,000		+204,000
b. One more day of pay		14,699,000		+57,000
c. Annualization of FY 1995 locality pay raise		14,699,000		+121,000
d. January 1996 pay raise		14,699,000		+249,000
e. FECF increase		14,699,000		+2,000
f. Payment for centrally furnished services		1,725,000		+283,000
g. Service and supply fund increase		655,000		+32,000
h. Increased cost of laboratory materials and supplies		7,406,000		+198,000
i. FTS 2000 reduction		36,000		-8,000
j. DHHS Working Capital Fund reduction		243,000		-38,000
Subtotal				+1,100,000

Summary of Changes continued

B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a) Noncompeting	1,235	277,359,000	-59	-7,710,000
b) Competing	355	75,912,000	+80	+21,028,000
c) SBIR/STTR	65	8,870,000	+1	+472,000
Subtotal	1,655	362,141,000	+22	+13,790,000
2. Special/Comp Centers	3	1,264,000	--	+43,000
3. Other research	129	10,147,000	+1	+355,000
4. Research Training	627	17,069,000	+4	+597,000
5. R & D Contracts	67	45,180,000	--	+1,600,000
Subtotal, extramural	2,481	435,801,000	+27	+16,385,000
	(FTEs)	Amount	(FTEs)	Amount
7. Intramural research	641	77,481,000	-7	-532,000
8. Research Management and Support	466	24,764,000	-4	-400,000
Total, changes			-11	+19,308,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Full-time equivalent employment.....	1,107	1,096	-11
Full-time equivalent of overtime and holiday hours................	1	1	---
Average ES salary..................	$108,453	$110,936	+$2,483
Average GM/GS grade.................	10.0	10.0	---
Average GM/GS salary................	46,228	47,286	+1,058
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	75,842	77,578	+1,736
Average salary of ungraded positions	28,778	29,437	+659
Personnel compensation:			
Permanent positions...............	$26,887,000	$27,786,000	+$899,000
Positions other than permanent....	6,412,000	6,626,000	+214,000
Other personnel compensation......	1,541,000	1,592,000	+51,000
Special personnel services........	3,753,000	3,879,000	+126,000
Subtotal, personnel compensation	38,593,000	39,883,000	+1,290,000
Personnel benefits..................	8,825,000	9,121,000	+296,000
Benefits for former personnel.......	63,000	64,000	+1,000
Travel and transportation of persons	1,112,000	1,144,000	+32,000
Transportation of things...........	181,000	186,000	+5,000
Rental payments to GSA.............	1,079,000	1,111,000	+32,000
Rental payments to others..........	353,000	363,000	+10,000
Communications, utilities and miscellaneous charges............	1,796,000	1,848,000	+52,000

Budget Authority by Object -- continued

Printing and reproduction..........	$236,000	$242,000	+$6,000
Consultant services................	160,000	160,000	---
Other services.....................	13,997,000	13,899,000	-98,000
Purchases from government accounts..	25,455,000	26,437,000	+982,000
Operation of GOCOs.................	---	---	---
R&D contracts......................	44,209,000	45,781,000	+1,572,000
Supplies and materials.............	7,429,000	7,645,000	+216,000
Equipment..........................	3,820,000	3,944,000	+124,000
Grants, subsidies & contributions...	390,621,000	405,406,000	+14,785,000
Insurance claims & indemnities......	117,000	120,000	+3,000
Total budget authority by object..	538,046,000	557,354,000	+19,308,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel compensation:			
Permanent positions (11.1)............	$26,887,000	$27,786,000	+$899,000
Positions other than permanent (11.3)..	6,412,000	6,626,000	+214,000
Other personnel compensation (11.5)....	1,541,000	1,592,000	+51,000
Special personnel services (11.8)......	3,753,000	3,879,000	+126,000
Total, personnel compensation (11.9)	38,593,000	39,883,000	+1,290,000
Personnel benefits (12.1)...............	8,825,000	9,121,000	+296,000
Benefits for former personnel (13.0).....	63,000	64,000	+1,000
Travel (21.0)...........................	1,112,000	1,144,000	+32,000
Transportation of things (22.0)..........	181,000	186,000	+5,000
Rental payments to others (23.2).........	353,000	363,000	+10,000
Communications, utilities and miscellaneous charges (23.3)..........	1,796,000	1,848,000	+52,000
Printing and reproduction (24.0).........	236,000	242,000	+6,000
Consultant services (25.1)...............	160,000	160,000	---
Other services (25.2)...................	13,997,000	13,899,000	-98,000
Purchases from government accounts (25.3)........................	22,051,000	22,934,000	+883,000
Operation of GOCOs (25.4)................	---	---	---
Supplies and materials (26.0)............	7,429,000	7,645,000	+216,000
Total................................	94,796,000	97,489,000	+2,693,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1995 House Report	
Asthma	
1. The House in its report 103-553, page 54, stated, -- "The number of asthma patients and the number of asthma-related deaths have increased dramatically in the past decade. The morbidity and mortality among minority populations are disproportionately high...Inner-city residents also suffer disproportionately from asthma. The Committee urges NIAID to continue its support for the National Cooperative Inner-City Asthma Study."	1. The National Institute of Allergy and Infectious Diseases (NIAID) is committed to reducing the burden of asthma among underserved minority populations in the United States. Several approaches have been taken to accomplish this goal. These include the development and implementation of the NIAID National Cooperative Inner-City Asthma Study (NCICAS), the establishment of NIAID-coordinated outreach and demonstration programs in conjunction with the NIAID-supported Asthma, Allergic and Immunologic Diseases Cooperative Research Centers, and the establishment of a series of asthma outreach and demonstration research grants. Preliminary results from the NIAID NCICAS have highlighted the complex and multi-faceted nature of this disease among inner-city children and demonstrated the value of a broad-based approach to intervention. NIAID has succeeded in implementing one such broad-based intervention in its eight-site inner-city asthma study. It is anticipated that the outcome of this effort will demonstrate the effectiveness of combining medical, educational, and environmental controls to reduce the burden of asthma in these inner-city populations.

Item	Action Taken or To Be Taken
1995 House Report	
	Future plans include the continuation of the NCICAS for an additional four years. The NIAID will continue to support demonstration and education projects within the Asthma Centers program and individual asthma research grants. This will enable the NIAID to assess the effectiveness of specific interventions, make necessary improvements and refinements, and apply culturally appropriate approaches to additional geographic locations and minority populations with asthma.
Microbicides	
2. The House in its report 103-553, page 53, stated, -- "The Committee acknowledges the commitment and leadership of NIAID in supporting research on the barrier methods for STDs/HIV prevention. The Committee believes that safe, effective topical microbicides are urgently needed to prevent the spread of STDs and HIV infection for both women and men. The Committee encourages NIAID to increase funding for the major areas of microbicide research, including basic research, product development, clinical evaluation, and behavioral research."	2. In FY 1994, the National Institute of Allergy and Infectious Diseases (NIAID) continued to support basic research on the molecular basis of the early steps in the infectious process of HIV infection and classical STDs. This research provides the basic foundation for developing effective strategies to interfere with host/pathogen interactions using chemical barriers. In FY 1995, NIAID is nearly doubling the funding level for Topical Microbicides research to support a multi-disciplinary research effort. Topical Microbicide Program Projects, to be awarded in FY 1995, will facilitate the development of a knowledge base that coordinately accounts for microbiological and host factors important in preventing sexually transmitted infections safely and effectively. NIAID will also fund new research on facilitating the development of diagnostic tests that are rapid, inexpensive, and easy to use. These tests will enable clinical research on microbicide evaluation to proceed rapidly and contribute significantly

Item	Action Taken or To Be Taken
1995 House Report	
	to reducing the costs of the clinical evaluations. Internationally, NIAID has established sites that provide immediate access to populations with high rates of HIV infection and STDs for evaluation of currently available chemical barriers as well as new microbicides.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1995 Senate Report	
Asthma	
1. The Senate in its report 103-318, pages 84 and 85, stated, -- "The number of asthma patients and the number of asthma-related deaths have increased approximately 87 percent in the past decade, and morbidity and mortality among minority populations are disproportionately high...The Committee urges NIAID to continue its support for the National Cooperative Inner-City Asthma Study, a network of eight sites which was started in 1991..."	1. Same response as number 1 in "1995 House Report", Asthma.
Microbicides	
2. The Senate in its report 103-318, page 85, stated, -- "The Committee acknowledges the commitment and leadership of NIH in supporting research on the barrier methods for STDs/HIV prevention and notes that three Request for Applications related to topical microbicides and chemical contraceptives were issued by NIAID and NICHD in FY 1994....The Committee encourages increased funding for the major areas of microbicide research, including basic research, product development, clinical evaluation, and behavioral research."	2. Same response as number 2 in "1995 House Report", Microbicides.

Item	Action Taken or To Be Taken
1995 Senate Report	
Cryptosporidium	
3. The Senate in its report 103-318, page 85, stated, -- "The Committee urges the NIAID to expand research into detecting cryptosporidium in drinking water, conducting dose response analyses, and developing treatments for cryptosporidiosis, particularly for immuno-compromised individuals.	3. We agree that improved diagnostics and treatment for cryptosporidiosis is warranted. In Fiscal Year 1995, the National Institute of Allergy and Infectious Diseases will support basic research and animal model development on cryptosporidial infections. We will support research aimed at characterizing cryptosporidial strains, disease expression and epidemiology, the molecular biology of the organism, passive antibody-mediated control of cryptosporidiosis, and the rational design and evaluation of drugs for anticryptosporidial activity.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amt. Authorized	1995 Appropriation	1996 Amt. Authorized	1996 Budget Request
Research and Investigation	Section 301	42§241	Indefinite--	$520,977,000	Indefinite--	$539,688,000
National Institute of Allergy and Infectious Diseases	Section 446	42§285f	Indefinite--		Indefinite--	
National Research Service Awards	Section 487	42§288-1	Such Sums as Necessary	17,069,000	Such Sums as Necessary	17,666,000
Total Budget Authority				$538,046,000		$557,354,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1987[2]	330,551,000	403,853,000	541,343,000	545,523,000
1988	551,102,000	439,667,000[3]	661,458,000	638,800,000
1989	435,084,000[4]	732,453,000[5]	758,352,000	744,152,000
1990	442,596,000[6]	845,523,000	847,112,000	843,745,000[7]
1990 Sequester				-10,768,000
1991	886,875,000	944,965,000	904,010,000	906,251,000[8]
1991 Sequester				-12,000
1992	976,711,000	972,830,000	965,952,000	959,914,000[9]
1993	1,010,845,000	990,055,000	989,055,000	979,471,000[10]
1994	1,065,583,000	1,065,583,000	1,065,583,000	1,063,704,000
1995	542,864,000[11]	535,847,000[12]	535,847,000[12]	535,847,000[12]
1996	557,354,000[11]			

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[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and appropriation spread the funding among the Institutes, including $145,850,000 for NIAID.

[3] Does not include funding for AIDS research. Consolidated at the Secretary's level.

[4] The 1989 request excludes funds for AIDS research ($310,268,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

[5] Excludes $13,537,000 in NRSA training programs not considered.

[6] The 1990 request excludes funds for the National HIV program ($400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

[7] Excludes enacted administrative reduction of $2,573,000.

7/ Excludes enacted administrative reduction of $2,573,000.

8/ Excludes enacted administrative reductions of $26,986,000.

9/ Excludes enacted administrative reductions of $11,197,000.

10/ Excludes enacted administrative reductions of $12,334,000.

11/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research.

12/ Excludes enacted administrative reductions of $308,000, $4,000, and $257,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Allergy, immunology and transplantation	---	$153,565	---	$154,725	---	$153,437	---	$158,152	---	$164,098	---	+$5,946
Microbiology and infectious diseases	---	259,866	---	267,861	---	269,326	---	277,649	---	288,088	---	+10,439
Subtotal.........	---	413,431	---	422,586	---	422,763	---	435,801	---	452,186	---	+16,385
Intramural research....	653	72,206	664	75,861	636	75,750	641	77,481	634	79,704	-7	+2,223
Research management and support..........	438	25,505	472	25,969	466	24,336	466	24,764	462	25,464	-4	+700
Total obligations......	1,091	511,142	1,136	524,416	1,102	522,849	1,107	538,046	1,096	557,354	-11	+19,308
Unobligated balance lapsing.............		---		113		8		---		---		---
Total, budget authority	1,091	511,142	1,136	524,529	1,102	522,857	1,107	538,046	1,096	557,354	-11	+19,308

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

Justification

National Institute of Allergy and Infectious Diseases

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
1,102	$522,857,000	1,107	$538,046,000	1,096	$557,354,000	-11	+$19,308,000

General Statement

Research supported by the National Institute of Allergy and Infectious Diseases (NIAID) continues to decrease or eliminate the burden of allergic and infectious diseases. The NIAID supports diagnostic, drug, and vaccine development that reduces the Nation's health care costs. These efforts have significantly benefitted the health of Americans, in particular, and they hold great potential for the developing world. Challenges abound, however, as we encounter new and re-emerging problems, such as acquired immune deficiency syndrome (AIDS), tuberculosis (TB), chronic fatigue syndrome (CFS), Lyme disease, and other emerging microbes. In addition, allergic diseases, including asthma, are currently among the major causes of illness and disability in the United States, affecting as many as 40 million Americans. These diseases result in considerable morbidity, mortality, pain and suffering; they result in absenteeism from work or school, and consequently, contribute to high medical care costs. The NIAID diligently strives to develop better ways to diagnose, treat, and prevent these illnesses.

We cannot overemphasize the intrinsic value of basic research in our search for research results that have immediate application to persons afflicted with disease. The information gleaned from fundamental research provides the basis for fashioning clinical and biological interventions; thus, we believe that investments in NIAID research will ultimately result in improved health and quality of life by improving the diagnosis, treatment, and prevention of diseases.

The President's appropriation request of $557,354,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NIAID research program during the last five years has been as follows:

	Amount	FTE
FY 1991	$475,063,000	1,005
FY 1992	511,142,000	1,091
FY 1993	524,529,000	1,136
FY 1994	522,857,000	1,102
FY 1995	538,046,000	1,107

Program Purpose and Method of Operation

Infectious diseases remain the most common cause of death for children worldwide, and disorders of the immune system affect more than 1 in 10 Americans. NIAID-supported biomedical research has advanced the prevention and treatment of diseases that result in a great cost to individuals and society. These advances reduce suffering and save lives, and they translate into economic cost savings by reducing the use of health care services and improving human productivity. The NIAID's mission is to conduct and support research and training aimed at alleviating suffering from these illnesses.

To accomplish this mission, NIAID supports research and training grants and contracts at many universities and medical centers in the United States. The Institute also conducts basic and clinical investigations in its intramural laboratories at Bethesda, Rockville, and Frederick, Maryland, and at Hamilton, Montana. The NIAID has three major non-AIDS research divisions: Allergy, Immunology, and Transplantation; Microbiology and Infectious Diseases; and Intramural Research.

Overall Budget Policy

The NIAID FY 1996 budget request for NIAID non-AIDS research is $557,354,000, an increase of $19,308,000, or 3.6 percent over the comparable FY 1995 level of $538,046,000. This request includes an increase of $1,000,000 targeted to tuberculosis, $3,333,000 targeted to prevention research, $1,500,000 targeted to structural biology and drug design, $1,500,000 targeted to disorders of developmental and reproductive biology, $500,000 targeted to gene therapy, and $300,000 targeted to the brain and brain disorders. Also, the budget request includes $355,000 for additional clinical center training and communications infrastructure improvements. The FY 1996 request will support 1,677 research project grants at $375,931,000, an increase of 22 awards and $13,790,000 over the FY 1995 comparable amount. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Noncompeting grants will receive an average increase of 4 percent over the FY 1995 direct cost level for recurring items of expense. The average cost of competing research project grants will increase by 4.2 percent, which is equal to the Biomedical Research and Development Price Index for FY 1996.

National Institute of Allergy and Infectious Diseases

Extramural Research

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$422,763,000	$435,801,000	$452,186,000	+$16,385,000

The NIAID supports research that prevents a broad spectrum of infectious diseases, disorders of the immune system, and allergic diseases. As a result, NIAID research reduces the impact of these diseases on public health. To achieve this outcome, the NIAID provides research grant, contract and cooperative agreement support to scientists at universities and other research institutions to conduct basic, applied, and clinical biomedical research. The Institute has drawn on its foundation of basic research to meet the scientific challenges posed by new and re-emerging health threats, such as AIDS, tuberculosis, Chronic Fatigue Syndrome, Lyme disease, and Hantavirus.

The NIAID Extramural Research Program is committed to supporting basic research studies on infectious and immunologic diseases. This basic research translates into prevention and treatment strategies for sexually transmitted diseases, asthma, allergies, parasitic, and fungal diseases; it results in improved diagnostics for infectious diseases and better evaluations of antiviral drugs; it fosters an improved understanding of transplantation immunology.

Funding for the NIAID Extramural Research program during the last five years has been as follows:

	Amount
FY 1991	$383,906,000
FY 1992	413,431,000
FY 1993	422,699,000
FY 1994	422,763,000
FY 1995	435,801,000

Rationale for the Budget Request

The FY 1996 budget request of $452,186,000 for the NIAID's extramural research programs represents an increase of $16,385,000, or 3.8 percent over the FY 1995 level. Within the FY 1996 request level, funds will support the following budget activities: Allergy, Immunology, and Transplantation for $164,098,000 an increase of $5,946,000, or 3.8 percent over the FY 1995 estimate of $158,152,000, and Microbiology and Infectious Diseases for $288,088,000, an increase of $10,439,000, or 3.8 percent over the FY 1995 estimate of $277,649. The following provides a brief overview of the research activities in these areas and describes some major research activities we will pursue in FY 1996:

Basic Research. The NIAID will foster basic research to reveal new methods of immune intervention and to unmask new approaches for treating and preventing human autoimmune, allergic, and inflammatory diseases. Basic research by NIAID-supported scientists in molecular structure and function, host/pathogen interaction, genetics, and physiological and biochemical processes of bacteria, viruses, fungi and parasites will lead to increased understanding of the body's protective needs. In addition, we will continue funding studies on microbial pathogens to further extend basic insights needed to identify specific protective factors and to examine mechanisms of emergence, infection, pathogenicity, and virulence.

Emerging Infectious Diseases. In FY 1996, the NIAID will expand its research programs in tuberculosis, Lyme disease, chronic fatigue syndrome, and hantavirus. Infectious diseases have continued to emerge in recent years, impinging on the public health and escalating health care costs. There are several reasons why new infectious diseases are emerging. Two important factors are biochemical changes in the microbial agent or vector population and changes in the human population or behavior. By supporting a broad portfolio of infectious diseases research, the NIAID is poised to achieve its research goals of understanding the epidemiology, pathogenesis, and microbiology of emerging infectious diseases. This understanding will lead to developing treatment and prevention regimens.

In FY 1996, NIAID will fund multi-disciplinary, coordinated research groups to investigate the elements that contribute to the emergence or re-emergence of viral diseases; to establish the factors influencing the infective process and the host response to infection, and to discover the ~~weakest link~~ in the virus cycle to focus our intervention strategies. These awards will focus on virology, immunology, and medical epidemiology studies. This initiative will include a particular focus on hantavirus, an emerging disease in the Southwestern part of the United States.

Tuberculosis (TB). In FY 1996, NIAID will continue to focus on the development of improved diagnostics, treatment, and vaccine strategies to control and prevent tuberculosis infection. Our TB research investment has increased from $3.5 million in FY 1991 to an estimated $31.1 million in FY 1995. These funds supported a comprehensive agenda tackling issues of basic biology and pathogenesis, drug and vaccine development, and diagnostics. The FY 1996 budget request includes an additional $1 million for basic research into TB pathogenesis.

Lyme Disease. In FY 1996, the NIAID will establish the framework for starting a clinical trial for improved therapy of late stage Lyme disease. We expect to issue an award focusing on antimicrobial treatments for chronic or late stage Lyme disease and another award for a diagnostic center to support the clinical trial.

Also, in FY 1996, we will capitalize on a recent finding identifying a novel mechanism that identifies variations in disease-causing bacteria. This new and novel mechanism has the potential for application to the agent that causes Lyme disease; consequently, this opens the door for vaccine development and improvement of diagnostic techniques.

Chronic Fatigue Syndrome (CFS). During FY 1996, NIAID will expand its use of a recently developed animal model for CFS. This animal model is of specific benefit to CFS research because human patients are reluctant to subject themselves to exercise and its exacerbation of fatigue. We will use the knowledge gained from this model in studies of humans, and it should help our understanding of the physiological basis of CFS. In addition, NIAID will continue supporting three CFS Cooperative Research Groups, which provide a multi-disciplinary, systematic, sustained approach to studying CFS and a means for evaluating promising treatment regimens under standardized control conditions.

Tropical Medicine. In FY 1996, the NIAID will recompete its Tropical Medicine Research Centers at overseas sites where tropical infectious diseases remain significant public health threats. These centers will conduct basic, applied, and clinical research on parasitic and mycobacterial diseases, and they will study enteric diseases caused by viral or bacterial agents.

In addition, the NIAID will continue supporting the International Collaborations in Infectious Diseases Research (ICIDR) program, which supports basic, field, and clinical research on diseases endemic to tropical areas. The NIAID will support research requiring access to populations of patients, pathogens and invertebrate vectors in the areas where the diseases are endemic. Toward this end, we have structured the ICIDR program to conduct most of its research effort in the endemic areas. The goal is to produce new insights that will lead to improved methods to control and prevent infectious diseases that predominate developing countries of the tropics and subtropics but that also may affect people living in industrialized countries.

Sexually Transmitted Diseases (STDs). The NIAID will support research aimed at developing diagnostic tests that are sensitive, specific, and use non-invasive, convenient samples. We will capitalize on a recent advance using molecular amplification in diagnostic tests, which has markedly enhanced sensitivity to 90-95 percent. One major advantage of this technique is the ability to detect the presence pathogens in urine samples as opposed to urogenital swabs.

Also, NIAID will encourage research to develop new, inexpensive, single-dose regimen antibiotics since non-compliance with seven day treatment protocols and the current cost of single-dose therapy are important factors in both transmission and development of complications.

The NIAID will continue to support its multi-disciplinary STD Cooperative Research Groups and individual research projects. This intervention-oriented research is working to prevent STDs in a variety of populations, including high-risk adolescents, active duty servicemen, and minority women. Also, this research aims to improve STD education programs for clinicians.

Vaccine Development. The NIAID is the center of vaccine research and development within the U.S. Public Health Service. The Institute provides support for Vaccine Evaluation Units that conduct phase I and phase II human trials of safety, protective immunity, and protective efficacy of candidate vaccines.

In FY 1996, the NIAID will continue to support its broad array of research projects developing and testing candidate vaccines for cholera, hepatitis, influenza, pertussis, STDs, tropical diseases, tuberculosis, and many other diseases. Also, the NIAID will recompete its Maternal Immunization Group to undertake phase I and phase II evaluations of maternal immunization candidate vaccines in child-rearing aged and pregnant volunteers. The goal is to develop new or improved vaccines for H. influenza type b, group B streptococcus, pneumococcus, meningococcus and respiratory syncytial virus in neonates and infants.

Transplantation. The NIAID will continue to support researchers studying stem cell biology, particularly the development of new methods to isolate and reproduce stem cells from bone marrow and blood, and we will pursue new opportunities for cellular therapy in bone marrow transplantation. We will pursue recent advances that provide opportunities in organ transplantation where the infusion of donor bone marrow cells promotes allograft tolerance in various models in rodents, pigs, and monkeys.

The NIAID will support researchers studying a cell in mouse bone marrow that promotes engraftment of highly purified stem cells. These studies will further characterize the profile and additional functional properties of marrow cells that aid stem cell engraftment to accelerate new applications for stem cell therapy in transplant tolerance. Also, we will pursue new leads to improved bone marrow·transplantation therapy in a variety of diseases such as leukemia and immune deficiency.

In FY 1996, NIAID will launch a new initiative to isolate and comprehensively characterize hematopoietic stem cells (HSC) from different tissue sites. This initiative will, in part, allow us to develop effective procedures that will aid solid organ graft survival.

Also, the NIAID will renew its cooperative clinical trials in transplantation program to evaluate the most promising tolerance inducing regimens for adult kidney transplant recipients. If we achieve this, kidney transplant recipients will no longer have to use toxic and expensive immunosuppressive drugs for the rest of their lives.

Moreover, NIAID will foster research to identify the molecules and mechanisms involved in chronic allograft rejection. Using recent advances in our understanding of transplantation immunology, we will urge clinicians and basic immunologists to pursue leads to develop agents, procedures, and protocols to predict, detect, treat, and prevent chronic rejection.

Asthma and allergic diseases. The NIAID will support investigations of gene abnormalities associated with the expression of asthma and allergic diseases.

Since these variants of the normal genes are the causes of asthma and hypersensitivity, we will foster new therapeutic intervention studies to target these genes and proteins.

We will renew a segment of our National Cooperative Inner-city Asthma Study (NCICAS). We will also fund small outreach and demonstration projects to translate the findings from the NCICAS to clinicians and individuals suffering from asthma.

Cost savings. The NIAID funds many research projects that result in cost savings or improves the quality of life of people inflicted with disease. The following is a sample of these research results:

Treatment of infants and children with congenital toxoplasmosis allows normal developmental outcomes: Each year approximately 1 in 1,000 infants born in the United States has congenital toxoplasmosis, a protozoan infection. Information concerning the appropriate evaluation, treatment and outcome of this disease has been limited. NIAID-supported investigators conducted a longitudinal study of treated infants and children over a 10-year period and compared them with untreated historical controls. The investigators documented the safety and feasibility of treating infants for one year with pyrimethamine and sulfonamides. The evaluation showed that 70 percent of the treated infants who had severe central nervous system impairment and eye pathology at birth developed normally and are currently functioning well. This study highlights the importance of prompt and early diagnosis and treatment of congenital toxoplasmosis.

Fluconazole vs. amphotericin B for treatment of non-neutropenic patients with candidemia: NIAID-supported investigators conducted a clinical trial of *Candida* bloodstream infections in hospitalized patients with vascular catheters, who were immunocompromised but non-neutropenic. Patients with positive *Candida* blood cultures and signs and symptoms of infection received either amphotericin B or fluconazole. The study proved that the newer antifungal drug, fluconazole, was as effective as amphotericin B but less toxic and easier to administer than amphotericin, which can have serious side effects. The study also showed the importance of replacing all catheters in such infected patients and the significant mortality caused by *Candida* in this patient population.

Findings of the National Cooperative Inner-City Asthma Study (NCICAS): Despite improved treatments, asthma-related illness and deaths have increased in the United States, particularly in minority populations. NIAID funded the NCICAS to identify risk factors for asthma in inner-city children and to develop ways to reduce these risks. The program has shown that the high rate of morbidity associated with childhood asthma in this population is a multifaceted problem that includes lack of access to health care, poor adherence, on the part of asthma sufferers, to required treatment regimens, and psycho-social stresses. Also, the study showed the important role that cockroaches play as an allergen in inner-city homes. One finding from the study is that assigning an asthma case manager and educational intervention is a cost-effective way to decrease asthma morbidity.

Advances in transplantation immunology: In bone marrow transplantation, the tissue being transplanted can attack the recipient, resulting in graft-versus-host disease (GVHD), a potentially fatal complication. In clinical trials, NIAID-funded scientists have achieved improved success by treating donor bone marrow, before infusion into the recipient, with a monoclonal antibody directed to CD6, a molecule present on certain T lymphocytes, thus eliminating these cells from the transplanted tissue. The trial showed that using this procedure, graft failure occurred in less than 3% of patients, GVHD decreased to 15%, and mortality decreased significantly - to less than 15% of bone marrow patients receiving standard treatment. The investigators achieved these results without using the standard toxic immunosuppressive agents.

National Institute of Allergy and Infectious Diseases

Intramural Research

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
636	$75,750,000	641	$77,481,000	634	$79,704,000	-7	+$2,223,000

The National Institute of Allergy and Infectious Diseases (NIAID) conducts in-house research through the Division of Intramural Research (DIR). DIR scientists study immunologic, allergic, and infectious diseases in NIAID's 16 laboratories located in Bethesda, Maryland at the main NIH campus with satellite laboratories in adjacent Rockville, Md. and Frederick, Md. and the Rocky Mountain Laboratories in Hamilton, Montana. The Bethesda facility also provides space for DIR's clinical activities at the NIH Clinical Center. Patients are frequently admitted to this clinical unit to participate in new and promising treatment or diagnostic procedures derived from the basic research conducted in DIR's laboratories.

Besides conducting research, DIR offers many laboratory and clinical research training opportunities for physicians and scientists who go on to positions of scientific leadership in universities across the country.

Comparable funding for the NIAID Intramural Research activity during the last five years has been as follows:

	Amount	FTE
FY 1991	$67,099,000	623
FY 1992	72,206,000	653
FY 1993	75,861,000	664
FY 1994	75,750,000	636
FY 1995	77,481,000	641

Rationale for the Budget Request

Transplantation. In FY 1996, NIAID scientists will continue studies on the structure of an immune cell protein that may be a useful target for drugs that aid tissue transplants or treat autoimmune diseases. Intramural scientists have deciphered the structure of a protein on the surface of immune cells, called natural killer (NK) cells, that play an important role in preventing these cells from destroying inappropriate targets.

Moreover, NIAID researchers will focus on learning the structure of the NK cell protein that turns off its killing action, allowing the scientists to develop drugs that stimulate this protein. This knowledge will allow us to improve transplant survival and treat autoimmune diseases.

Immune Disorders. Intramural scientists will investigate a recently discovered disorder in children that involves the over production of an unusual class of immune cells. The discovery of this disorder will help researchers understand the role of these cells and of various immune system chemicals. Symptoms of the disorder include enlargement of the liver and spleen, destruction of red blood cells by immune cells, and inflammation of the kidney. Currently, the only treatment for this disorder is to remove the enlarged spleen. NIAID scientists, however, will conduct studies to block over production of the immune cells in hopes of discovering alternatives to such drastic measures.

Intramural scientists recently characterized a genetic mutation responsible for an immunodeficiency disease in mice that is similar to the human disease in which patients have a complete arrest in the development of B lymphocytes--the immune cells that produce antibodies. As a result, they are susceptible to repeated severe infections with bacteria such as streptococci, pneumococci, and *Hemophilus influenzae*. In FY 1996, NIAID scientists will conduct studies to better understand the mechanisms of B lymphocyte development and the treatment for immunodeficiency diseases.

Chronic granulomatous disease (CGD). Intramural scientists will continue their research to develop a mouse model that can carry a gene for CGD. The development of an animal model of this disease will allow researchers to study in greater detail the mechanisms of CGD and to test possible gene therapies.

Sexually Transmitted Diseases. Intramural scientists will refine their recently developed highly sensitive and non-invasive assay for detecting chlamydial infections in symptomatic and asymptomatic men and women. The assay uses urine samples to screen for the presence of chlamydial DNA. When fully implemented, the assay could detect early chlamydial infections in men and women and prevent the infection's adverse consequences.

Vaccine Development. The NIAID will continue its evaluation of candidate respiratory and gastrointestinal vaccines in humans for safety, immunogenicity, genetic stability, and efficacy. In addition, we will conduct studies to find out the optimal dosage and schedule for these vaccines. Moreover, in FY 1996, we will continue our funding of vaccine studies focusing on respiratory viruses, parainfluenza, rotavirus, and genital herpes.

Tuberculosis. Intramural scientists will conduct studies to develop cytokine treatments for patients with drug-resistant tuberculosis. This research will form the basis for deciding the optimal treatment regimen and for detecting the conditions leading to drug resistance.

Lyme disease. In FY 1996, NIAID scientists will establish a collaborative intramural/extramural research team to formulate and test stringent criteria for Lyme infection, obtain a comprehensive medical, psychiatric, microbiologic, and immunologic profile of patients with chronic Lyme infection, develop a prospective pilot database on infected patients and their treatment, and conduct a multi-center placebo-controlled therapeutic trial.

Hepatitis E. Intramural scientists will pursue the feasibility of developing a hepatitis E vaccine for humans based on a recent NIAID discovery. Intramural researchers showed that immunization of cynomolgus monkeys with a recombinant hepatitis E virus capsid protein protected the animals completely against hepatitis E disease. Immunization prevented or greatly decreased the quantity of virus in the feces and completely protected against abnormal liver histopathology and viremia. These observations establish the feasibility of developing a hepatitis E vaccine for humans, and NIAID investigators will pursue these leads in FY 1996.

Cost Savings. There are many cost savings and improvements to the quality of life emanating from NIAID intramural research. A sample of these research results follows:

Vaccine for treating genital herpes reduces the number of recurrent infections in infected individuals: An experimental vaccine has safely reduced by one-third the number of genital herpes outbreaks in people with previous recurrences of the disease. Recent studies by NIAID intramural researchers and others showed that an immunotherapeutic vaccine designed to enhance the body's immune response to herpes simplex virus 2 (HSV-2) could modify the course of the disease. In the studies, the vaccine significantly reduced the monthly rate and total number of outbreaks, and it prolonged the time to the first recurrence when compared with a placebo. HSV-2 infects over 25 million Americans; 10 million Americans have recurring HSV genital infections each year.

Interferon gamma boosts ability to fight drug-resistant mycobacterial infections: Laboratory and animal studies have suggested that interferon gamma, a protein normally secreted by the immune system's T cells, plays an important role in containing and clearing certain infections in the body. NIAID intramural investigators showed that interferon gamma produced dramatic clinical benefits in patients with non-tuberculous mycobacterial infections who did not respond to conventional therapies. The patients suffered from a drug resistant strain and had received the maximum tolerated conventional treatment for at least four months before enrolling in the study. All patients treated with interferon gamma rapidly improved and many of their symptoms abated. Non-tuberculous mycobacteria can cause serious life-threatening diseases such as disseminated *Mycobacterium avium* complex (MAC), which affects up to 40 percent of people infected with human immunodeficiency virus.

National Institute of Allergy and Infectious Diseases

Research Management and Support

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
466	$24,344,000	466	$24,764,000	462	$25,464,000	-4	+$700,000

The Research Management and Support (RMS) activity provides the resources that contribute to the general management and policy direction of the Institute's extramural programs. The managerial, scientific, and administrative functions encompassed by this activity include grants and contracts management, the scientific review of grant and contract applications, scientific program management, financial management, program planning and development, personnel, information dissemination, data management, procurement, property, and technology transfer.

Funding for the Research Management and Support activity during the last five years has been as follows:

	Amount	FTE
FY 1991	$24,058,000	382
FY 1992	25,505,000	438
FY 1993	25,969,000	472
FY 1994	24,344,000	466
FY 1995	24,764,000	466

Rationale for the Budget Request

The FY 1996 NIAID budget request for the Research Management and Support budget activity is $25,464,000, an increase of $700,000 from the 1995 estimate.

In FY 1996, NIAID management will continue to reassess the state of science in those areas within the Institute's purview. These efforts will include the review of progress and the identification of areas of unusual scientific opportunity that may lead to new approaches to support and help research. Vital to these efforts is the continued participation in and sponsorship of selected meetings, conferences, workshops, and symposia on high-priority research topics and issues, including areas of technology transfer and consensus development. These activities provide the necessary forum to exchange and foster new information, and to translate research findings to clinical care.

NIAID will draw upon the advice and counsel of its task forces, national advisory groups, blue ribbon panels and other outside experts in the development and refinement of the Institute's scientific agenda. This methodology was extremely beneficial in the development of the NIAID Tuberculosis Agenda and the Vaccine Development Initiatives Plan.

We will continue to emphasize outreach activities directed to health professionals, voluntary associations, and various private sector groups that extend to lay audiences or at-risk groups. The Institute will continue to work closely with minority professional associations, medical facilities and academic institutions to distribute information on the diseases and disorders that disproportionately affect minority populations; encourage young minority scientists to participate in the Institute's scientific mission; and to reach out to the minority scientists of tomorrow through its several student programs.

National Institute of Allergy and Infectious Diseases
Detail of Full-Time Equivalent Employment (FTE)

	FY 1994 Actual	FY 1995 Estimate	FY 1996 Estimate
Office of the Director.......	162	162	161
Division of Intramural Research..................	636	641	634
Division of Extramural Activities................	105	105	104
Division of Allergy, Immunology, and Transplantation..........	19	19	19
Division of Acquired Immunodeficiency Syndrome..	124	124	123
Division of Microbiology and Infectious Diseases....	56	56	55
TOTAL NIAID.............	1,102	1,107	1,096

Average GS/GM Grade

1991	10.0
1992	10.1
1993	10.0
1994	10.0
1995	10.0
1996	10.0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Allergy and Infectious Diseases
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive level I............	--	--	--
Executive level II...........	--	--	--
Executive level III..........	--	--	--
Executive level IV...........	--	--	--
Executive level V............	--	--	--
Subtotal.................	--	--	--
Total - Exec. Level Salary....	--	--	--
ES-6.........................	0	0	0
ES-5.........................	3	3	3
ES-4.........................	7	8	8
ES-3.........................	3	2	2
ES-2.........................	1	1	1
ES-1.........................	0	0	0
Subtotal.................	14	14	14
Total - ES Salary............	$1,489,300	$1,518,335	$1,562,291
GS/GM-15.....................	65	62	62
GS/GM-14.....................	98	94	94
GS/GM-13.....................	88	94	94
GS-12........................	104	105	102
GS-11........................	117	120	117
GS-10........................	2	2	2
GS-9.........................	73	73	71
GS-8.........................	25	25	25
GS-7.........................	86	87	85
GS-6.........................	57	57	56
GS-5.........................	13	14	14
GS-4.........................	7	7	7
GS-3.........................	2	2	2
GS-2.........................	3	3	3
GS-1.........................	0	0	0
Subtotal.................	740	745	734

	1994 Actual	1995 Estimate	1996 Request
Grades established by Act of July 1, 1994 (42 U.S.C. 207)			
Assistant Surgeon General....	1	1	1
Director Grade..............	0	0	0
Senior Grade................	34	34	34
Full Grade..................	14	14	14
Senior Assistant Grade.......	29	29	29
Assistant Grade.............	4	4	4
Subtotal...............	82	82	82
Ungraded...................	32	32	32
Total Permanent Positions....	868	873	862
Total Positions, End of Year.	1,084	1,089	1,078
Total Full-Time Equivalent (FTE) Employment, End of Year	1,102	1,107	1,096
Average ES level............	3.9	3.9	3.9
Average ES salary...........	$106,379	$108,453	$110,936
Average GS/GM grade.........	10.0	10.0	10.0
Average GS/GM salary........	$45,344	$46,228	$47,286

TUESDAY, MARCH 14, 1995.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

DR. KENNETH OLDEN, DIRECTOR
CHARLES E. LEASURE, JR., ASSOCIATE DIRECTOR FOR MANAGEMENT
LAURIE JOHNSON, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. The subcommittee will come to order.

We are pleased to welcome Dr. Kenneth Olden, the Director of the National Institute of Environmental Health Sciences, this afternoon. Dr. Olden, why don't you introduce the people who are at the table with you and then proceed in any way you wish.

INTRODUCTION OF WITNESSES

Dr. OLDEN. You know the people to my right. To my left is the Associate Director for Management, Mr. Charles Leasure; and to his left is the budget officer, Ms. Laurie Johnson.

Mr. PORTER. Thank you.

OPENING STATEMENT

Dr. OLDEN. Mr. Chairman, committee Members, I am pleased to appear to discuss the important work that the National Institute of Environmental Health Sciences does to prevent human disease. Humans are exposed to a wide variety of environmental agents from conception to death. While it has already been established that some of these agents have obvious and significant health effects, the full extent of the contribution of the environment to human disease and dysfunction is an area of health research that requires attention.

Environmental health science research, with its focus on fundamental science and prevention, is important for the development of rational and cost-effective public health and regulatory policies related to environmental protection. Environmentally related diseases are preventable, yet they impose a major burden on society in terms of human suffering and costs related to health care.

In addition to the Institute's orientation toward prevention and fundamental research, we also support the development and validation of new technologies through our applied research program.

Examples of our applied research activities include the development of, first, new models and technologies to improve risk assessment and screening for environmental carcinogens and toxins; second, a promising new technology to improve the efficiency of destruction of hazardous substances during incineration; three, new approaches to bioremediation involving genetically engineered microorganisms; and, finally, the development of a steam injection technology to remove solvents and liquid fuels from soil contaminated by leaks in underground storage tanks or spills on the surface.

This has been a very good year for the Institute. One of our scientists, Dr. Martin Rodbell, was the corecipient of the 1994 Nobel Prize in Medicine for his discoveries on how chemical signals are translated into biological processes, such as growth and proliferation. Such fundamental research is critical to understanding how environmental agents disrupt cellular signaling or communication mechanisms that govern important biological processes.

Another research highlight of the Institute was the isolation of the long sought-after breast cancer gene, BRCA–1. Through the collaborative efforts of scientists at NIEHS, with a team at the University of Utah, isolation of BRCA–1 gene is a landmark discovery in that we are now closer to understanding the etiology of breast cancer and opportunities to develop a screening test to identify individuals with mutations in this gene are greatly improved. Efforts are already under way to develop animal models of human breast cancer to probe the role of environmental agents in the etiology of this disease.

Another exciting finding has been the development of mouse models that both over and underexpress the estrogen receptor. Animals without estrogen receptors, with a normal number of receptors and with twice the number of receptors are powerful tools to investigate the role of natural and environmental estrogens in the etiology of cancers of the breast, the uterus, ovaries and testicles, and also the decline in sperm count and developmental abnormalities of the reproductive tract. Efforts are already under way to create mice expressing human estrogen receptors.

Finally, scientists at NIEHS recently discovered a model DNA repair process in human cells. DNA repair, or copy editing, is critical for the protection and integrity of the information encoded in the human genome. Genetic material in humans is constantly under attack both by normal metabolic processes occurring in our cells and by insults from external environmental agents like radiation or chemicals. The resulting DNA damage is usually removed by a variety of DNA repair processes. Unrepaired DNA damage can lead to mutations in genes causing a wide variety of diseases, including cancers.

Research on DNA repair may be important in developing public health policy related to protection from environmental hazards. For example, the considerable variability and DNA repair capacity among individuals or populations may explain, at least in part, why chemicals or physical agents found to be carcinogenic or toxic to some individuals are less or more active in others. These studies may lead to the development of diagnostic tests for defective DNA repair genes which could save lives by limiting exposures to known DNA damaging agents or through early detection and treatment.

The Institute is poised to make substantial breakthroughs in several areas. First, elucidation of the role of BRCA–1 in the etiology of breast cancer; second, elucidation of the role of estrogens in the development of cancers and other diseases and dysfunctions; third, development of a strategy to prevent aflatoxin B1-induced liver cancers based on the prophylactic use of the drug oltipraz; fourth, the development and validation of alternative models and test systems for detecting environmental carcinogens and toxins.

The goal of this research is to develop and validate new models and test systems to reduce the current dependency on the costly rodent bioassay. Preliminary results suggest that models can be developed that are less costly and can be performed more rapidly.

Finally, the areas of lead poisoning treatment and prevention and susceptibility of children to environmental toxins will remain a special interest of the Institute.

In summary, the Institute's compelling mission, high quality research and efficient management, make this a very wise investment. The President's request for fiscal year 1996 is $278,832,000. I would be happy to answer any questions that you might have.

[The prepared statement and biography of Dr. Kenneth Olden follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Environmental Health Sciences

Mr. Chairman, committee members, I am pleased to appear before you to discuss the important work the National Institute of Environmental Health Sciences does to prevent human disease. Humans are exposed to a wide variety of environmental agents from conception to death. These factors include: foods and nutrients, physical agents such as heat and ionizing and non-ionizing radiation, social and economic factors, lifestyle choices and substance abuse, and synthetic and naturally-occurring chemicals. While it has already been established that some of these agents have obvious and significant health effects, the full extent of the contribution of environmental agents to human disease and dysfunction is an area of health research that requires attention.

Economic and Public Health Impact of the Institute's Programs

Environmental health science research, with its focus on fundamental science and disease prevention, is important for the development of rational and cost-effective public health and regulatory policies related to environmental protection. Environmentally-related diseases are preventable, yet they impose a major burden on society in terms of human suffering and costs related to health care. If only five to ten percent of cancers are caused by the environment, this would account for 50,000 to 100,000 new cases of cancer each year in the U.S. alone. The impact of prevention of the environmental contribution to human morbidity and mortality takes on even greater significance when a similar proportion of other diseases and dysfunctions with environmental risk factors requiring medical intervention, (e.g., asthma, neurobehavioral abnormalities, birth defects and reproductive anomalies) are factored into the equation defining the health care savings.

New Technologies Developed with Support Provided by the Institute

In addition to the Institute's orientation toward prevention and fundamental science, we also support the development and validation of new technologies through our applied research programs. Examples of our applied research activities include the development of: (1) new models and methodologies to improve human risk assessment and screening for environmental carcinogens and toxins, (2) a promising new technology to improve the efficiency of destruction of hazardous substances during incineration, (3) new approaches to bioremediation using genetically-engineered microorganisms, and (4) the development of a steam injection technology to remove solvents and liquid fuels from soil contaminated by leaking underground storage tanks or spills on the surface. Laboratory and small scale tests of the steam injection technology were promising enough that the Department of Energy (DOE), Office of Environmental Restoration and Waste Management, invested $12,200,000 in a demonstration facility to clean up a 20-year-old gasoline spill at Lawrence Livermore Laboratory. The technology proved to be so successful that over 7,000 gallons of gasoline have been recovered and sent to a recycler for resale. Gasoline recovery rates were 60 times greater than those obtained by other methods currently used. The Department of the Navy will be using this technology to clean up soil contaminated by several toxic spills at the Alameda Naval Air Station and DOE is considering this technology for cleaning up a trichloroethylene spill at the Idaho National Engineering Laboratory.

Research Advances

NIEHS Scientist Emeritus and former Scientific Director, Dr. Martin Rodbell, was the co-recipient of the 1994 Nobel Prize in Medicine. Dr. Rodbell and Dr. Alfred Gilman, a grantee of the National Institute of General Medical Sciences, won the Nobel Prize for their discoveries on how chemical signals are translated into biological processes such as growth and proliferation. Cellular communication networks are frequent targets for many environmental agents. Such fundamental research is critical to understanding how environmental agents disrupt cellular signalling or communication mechanisms that govern important biological processes. During Dr. Rodbell's leadership as Scientific Director, he assembled a team of world class researchers interested in this area of investigation, which promises intellectual and scientific leadership for years to come.

Another significant advance is the isolation of the long sought-after breast cancer susceptibility gene, BRCA1, through the collaborative efforts of NIEHS intramural scientists with a team at the University of Utah, led by Dr. Mark Skolnick, a grantee of the National Cancer Institute and National Center for Human Genome Research. An inherited susceptibility to breast cancer due to mutations in BRCA1 is thought to account for about 5 percent of overall cases and 25 percent of the so-called early-onset cases (women under age 30). Isolation of the BRCA1 gene is a landmark discovery in that we are now closer to understanding the etiology of breast cancer, and opportunities to develop a screening test to identify individuals with mutations in this gene are greatly improved. Efforts are already underway to develop animal models of human breast cancer to probe the role of environmental agents in the etiology of this disease.

Other recent NIEHS advances include work on an estrogen receptor "knockout mouse". The female hormone, estrogen, directs and controls cell growth and differentiation by binding to important estrogen receptor proteins located in tissues throughout the body. Many environmental compounds bind to these same receptor proteins, thus potentially acting as "environmental estrogens." These environmental compounds may play a role in a wide range of diseases. In women, they may be implicated in development of endometriosis, uterine fibroids, and cancers of the breast, uterus, and ovaries. In men these compounds might explain the increase in testicular cancer, decline in sperm count and other reproductive tract anomalies. Using molecular biology approaches, one can develop animal models that over- or under-express protein products of specific genes. NIEHS intramural scientists, collaborating with researchers at the University of North Carolina at Chapel Hill, have developed mice that lack estrogen receptors. This will aid in the investigation of the role of environmental estrogens in the etiology of the above diseases and dysfunctions.

NIEHS is also interested in understanding the link between DNA repair processes and human disease. DNA repair or "copy editing" is critical for the protection and integrity of the information encoded in the human genome. Genetic material in humans is constantly under attack, both by normal metabolic processes occurring in our cells and by insults from external environmental agents like radiation or chemicals. The resulting DNA damage is usually removed by a variety of DNA repair processes. Unfortunately, these processes do not operate with perfect efficiency, especially in persons who have inherited a gene defect that is important for repair. Unrepaired DNA damage can lead to mutations in genes, causing a wide variety of diseases.

Research on DNA repair has flourished recently at the NIEHS and elsewhere and may be important in developing public health policy related to protection from environmental hazards. For example, the considerable variability in DNA repair capacity among individuals or populations may explain, at least in part, why chemicals or physical agents found to be carcinogenic or toxic in some individuals are less or more active in others. Thus, understanding the DNA repair process could lead to an environmental health policy that takes into account differences in capacity to repair damaged DNA. Furthermore, these studies may lead to the development of diagnostic tests for defective DNA repair genes which could save lives by limiting exposure to known DNA damaging agents or through early detection and treatment.

Scientists at the NIEHS recently discovered a previously unknown DNA repair process in human cells and are now searching for the genes required for this repair process. Defective DNA repair is implicated in a broad spectrum of cancers including a common form of colon cancer. Institute scientists are particularly interested in studies to determine the likelihood of a person being preconditioned for environmentally-induced diseases by inheriting one good copy and one defective copy of a critical repair gene. If such "genetically susceptible" persons knew they had greater than average risk, they could employ prevention strategies and avoid high-risk behavior. They could also be screened for disease more frequently, thus permitting earlier detection and treatment.

Finally, a public health success story made possible by the research supported by the NIEHS and other federal agencies. In July of 1994, the Centers for Disease Control and Prevention reported that in children ages one through five the mean blood lead levels had declined by 76 percent, from 15 to 3.6 micrograms per deciliter of blood, between 1978 and 1991. The percent of children with blood lead levels of 10 micrograms per deciliter of blood decreased from 88 percent to 9 percent. These are tremendous improvements in our children's health because NIEHS-supported research has shown that at blood lead levels higher than 10 micrograms per deciliter, children experience measurable decreases in intelligence and increases in neurobehavioral problems. Unfortunately, socioeconomically disadvantaged children living in urban environments have not experienced a significant decrease in the incidence of lead poisoning.

The identification of lead as a hazard and increased public awareness of the neurotoxic nature of lead has resulted in the phase-out of its use in gasoline and paint over the past 25 years.

Anticipated "Breakthroughs" in the Immediate Future

The Institute will continue exploring the role of estrogens in the development of cancers and other diseases and dysfunctions. In the coming year the NIEHS will focus on the following areas: (1) Defining the relationship of interactions between BRCA1, the breast cancer susceptibility gene, and environmental agents to the development of breast cancer. (2) Exploring links between estrogens and the world-wide increase in testicular cancer. Testicular cancer, typically a disease of young men rather than the elderly, has increased by 2-4 fold in industrialized countries over the past 50 years. Estrogens are a suspected risk factor based on the increased incidence of testicular cancer observed in male offspring of pregnant mice exposed to high doses of estrogens. Also, wildlife exposed to high levels of chemicals with estrogen-like activity develop mammary and testicular cancers. (3) Defining the relationship between exposure to estrogenic substances and the development of endometriosis, and endometrial, vaginal and ovarian cancers. (4) Understanding the relationship between exposure to estrogenic substances and the decrease (30 to 50 percent) in sperm counts, development of anomalies of the male reproductive organs, and the decline in birth rate.

Prevention of environmentally induced diseases remain a major focus of NIEHS research. In support of this goal, a molecular intervention study of aflatoxin B_1-induced liver cancer will start soon. NIEHS is supporting an intervention study to see if prophylactic use of the drug, oltipraz, prevents aflatoxin-induced liver cancer. This study is part of a series of complementary efforts by the NIEHS and the NCI examining the molecular basis of aflatoxin-induced cancer and the possibility of using oltipraz to intervene in development of this cancer.

The development and validation of alternative models and test systems for detecting environmental carcinogens and toxins will continue. The goal is to develop and validate new models and test systems to reduce the current dependency on the costly rodent bioassay. Preliminary results suggest that models can be developed that are less costly and can be performed more rapidly. Such test systems will allow for screening of dozens of chemicals annually.

The area of lead poisoning treatment and prevention is of special interest. NIEHS and the NIH Office of Minority Health Research are collaborating on research on the most vulnerable targets of lead toxicity, children. Clinical trials on the chelating agent, Succimer, are examining this compound's ability to prevent the neurobehavioral deficits observed from low lead exposures. Other projects explore the role of what might be a child's most important source of environmental lead--its mother. During pregnancy and lactation, the lead stored in a woman's bones might be mobilized and absorbed by her child. Two studies examine the distribution of lead during these critical periods, one in humans and one in primates. Results of these studies will help clinicians decide how best to treat pregnant women and protect developing fetuses from lead exposure.

Partnerships with Other Federal Agencies

The NIEHS manages and provides scientific oversight to approximately $80 million worth of environmental research programs developed through collaborative arrangements with other agencies, including DOE, EPA, and other HHS agencies.

Summary

The programs supported by the NIEHS are consistent with the goal of prevention of human disease and disability, and aid in the formation of economic growth and promotion of public/private partnerships. The Institute's compelling mission, high quality research and efficient management make it a wise investment at this time. The President's request for FY 1996 is $278,832,000. I would be happy to answer any questions.

OLDEN, DR. KENNETH

Director, National Institute of Environmental Health Sciences (NIEHS) and Director, National Toxicology Program (NTP)

July 22, 1938. Parrottsville, Tennessee

Education: B.S., Knoxville College, 1960; M.S., University of Michigan, 1964; Ph.D., Temple University, 1970 (research done in absentia at the University of Rochester).

Professional History: 1964-65, Research Assistant, Department of Biological Chemistry, Columbia University. 1970-74, Research Fellow and Instructor of Physiology, Harvard University Medical School. 1974-77, Senior Staff Fellow, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1977-78, Expert (Biochemistry) Division of Cancer Biology and Diagnosis, National Cancer Institute. 1978-79, Research Biologist, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1979-82, Associate Director for Research, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1982-84, Associate Director for Research and Deputy Director, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1984-85, Associate Director for Basic Research and Deputy Director, Howard University Cancer Center, and Professor of Oncology, Howard University Medical School. 1985-91, Director of the Howard University Cancer Center and Professor and Chairman of the Department of Oncology, Howard University Medical School. 1991-present, Director, NIEHS and NTP.

Professional Organizations: American Society for Cell Biology; American Society of Biological Chemistry; American Association of Cancer Research; Society for Biological Response Modifiers; Metastasis Research Society.

Honors, Awards: Porter Development Postdoctoral Fellow, 1970. NIH Postdoctoral Fellow, 1970-73. Macy Faculty Fellow, 1973-74. Citation Classic, Current Contents, Life Sciences, 1980. Member, Division of Cancer Biology and Diagnosis Board of Scientific Counselors, National Cancer Institute, 1981-85. Member, Public Policy Committee of the American Society for Cell Biology, 1984. Co-Chairman, Mid-Atlantic Region of National Black Leadership Initiative on Cancer, 1987-89. Member, Board of Directors, Association of American Cancer Institutes, 1987-90. Member, Division of Cancer Treatment Board of Scientific Counselors, National Cancer Institute, NIH, since 1988. Selected as "One of sixteen historical and contemporary role models" for the Museum of Science and Industry exhibit on Black Achievers in Science, Museum of Science and Industry, Chicago, IL, 1988. Member, Board of Directors of Association of Minority Health Professions Schools, 1988-present. Member and Co-Chairman of National Advisory Committee on Socio-Economically Disadvantaged of The American Cancer Society, 1988. Member, Advisory Panel Council for Cell Biology, National Science Foundation, 1989-90. Presidential appointment to membership on the National Cancer Advisory Board, 1991. Associate Editor of Cancer Research, The Journal of the National Cancer Institute, Cell Regulation, and Environmental Health Perspectives. Elected to membership in the Institute of Medicine in 1994.

Mr. PORTER. Dr. Olden, thank you very much for your good statement.

UNDERSTANDING ENVIRONMENTAL LINKS TO CANCER

Obviously, we are very pleased that one of your intramural researchers received the Nobel prize last fall. Several weeks ago we had Nobel laureates, six of them, before our subcommittee. At that time Dr. Michael Bishop, one of the Nobel laureates, in responding to a question about the environmental causes of cancer, said that he felt that we are as likely to understand the environmental links to cancer by mapping genetic damage that leads to cancer as we are by conducting epidemiological studies. How do you respond to his comments?

Dr. OLDEN. Mr. Chairman, I concur with Dr. Bishop's assessment. One of the efforts that I have been making since I have been Director of the Institute is to place greater emphasis on understanding mechanisms of action by taking advantage of new developments and new technologies in molecular biology.

Historically we have depended, often very heavily, on rodent carcinogenicity bioassay and epidemiological studies in humans, usually humans that had been exposed to environmental agents occupationally. While that data is important, I think it is much more important and more meaningful if we have not only information from animals and human epidemiological studies, but if we understand mechanisms of action at the molecular level. I think that is the approach, the way to go.

Also, if we have assay systems that let us look at processes at the molecular level, we can do dosimetry studies. In other words, we can do studies at low doses. The problem with both epidemiological associations and with rodent bioassays is that they are done at very high doses, at doses that individuals typically are not exposed.

COLLABORATION WITH OUTSIDE GROUPS

Mr. PORTER. Last month, NIH resolved the patent dispute involving the breast cancer gene, BRCA–1, that you have mentioned several times. Two other parties to the discovery have filed patent applications without crediting the NIEHS' scientists involved. Although this particular dispute has been resolved, does it highlight underlying issues that will continue to complicate NIH's collaboration with outside groups?

Dr. OLDEN. Well, maybe I should let Dr. Varmus answer that.

Dr. VARMUS. I think the answer to that could be yes. That is, it is difficult to understand why NIH scientists were excluded from the original patent application. But it is possible that one of the reasons was some reluctance to have NIH involved in the further licensing and commercialization of the products because of anxiety about the role of NIH and the control of pricing of any products.

NEW TESTING METHODS

Mr. PORTER. Dr. Olden, each year in hearings we discuss the backlog of chemicals that have not yet been tested for health safety. It is likely the backlog will always exceed your available resources. As part of your Reinventing Government exercise, have you developed any new ways to handle testing, for instance developing methods that would shorten testing times or set new priorities in determining which chemicals are selected for testing?

Dr. OLDEN. The answer is yes. The current benchmark for carcinogenicity testing is the two-year rodent bioassay. Two years is a long time and also it costs anywhere from $2 to $4 million per test. At that rate, we can only test a very few chemicals. It is estimated that there are 72,000 chemicals in commercial use in the U.S. today. Most of those chemicals do not need to be tested, but of the number that do need to be tested, we will never test them at the rate of 4, 10, 15 or even 20 per year. The way around that is to develop new tests that are faster and cheaper.

We have three approaches that are in development and others can be developed, obviously, that we think will get us around that problem. First of all, we are developing animals we call them transgenic mice—that will develop tumors in a period of six months rather than two years, and these animals are simply made more sensitive. In one case an activated oncogene is put in; in the other case one of the alleles of a suppressor gene is knocked out. So the animal is simply more sensitive.

When exposed to a carcinogen, these two strains of mice will develop cancers in six months, not two years. And both animals are useful in identifying both genotoxic, that is carcinogens that cause mutations, and those that do not cause mutations. In addition, there are animal models being developed that will allow us to do mutagenicity testing, that is, test for environmental agents that cause mutations in an animal. Typically, this is done in a bacterium. The problem with doing it in a bacterial system is that it does not provide one with an opportunity to explore mechanisms. So we have two systems, two animal models already in hand that we think will greatly improve testing in terms of cost and time.

There is a third development, and that is the incorporation of human genes into a bacterial system. For example, two genes have already been incorporated, genes for human detoxifying enzymes—some P–450's—and genes for human DNA repair enzymes.

One of the objections with the bacterium mutagenicity test is that the mutations occur in a background where there are no human systems, enzyme systems, but now we can put those in. So I think there are at least three approaches. We can definitely develop models that are much more effective.

Also, I think we can begin to do functional toxicology. In other words, screen for inhibition of known functions. I think we can also begin to use computer-based technology to predict based on structural function similarities. We have a large database now in excess of 450 chemicals. So the answer is yes, I think we can—we just need to make the investment to do it.

COMPARISON WITH OTHER AGENCIES

Mr. PORTER. In the past we have talked about your Institute's mission as compared to the Cancer Institute. Can you describe how you differentiate your research from that done by the National Center for Environmental Health at CDC and the research conducted by the Environmental Protection Agency?

Dr. OLDEN. Yes. Well, first of all, I think the National Center for Environmental Health does very little research, especially not laboratory research or toxicological testing. And the Environmental Protection Agency does mission-oriented research, short-term research, that is directed towards some immediate goal. At NIEHS, we do basic research that is long-term. It is not mission-oriented. In other words, there is not a project that we are trying to find an answer to. It is peer-reviewed. It is mainly university-based, whereas the EPA research is mainly in-house and on contracts.

We develop a lot of new methodologies and technologies, whereas the EPA is less interested in that because the standard they have to regulate uses the rodent bioassay. So they are less interested in developing new methodologies of the kind I just described to you. I would say that those are probably the main differences.

Now, with NCI, we are more interested in the role of environmental agents in the etiology of disease. We are concerned about genes only as they relate to gene environment interactions. When we have similar interests as the National Cancer Institute we will collaborate, and occasionally, they will also be interested in some aspect of an environmental agent and we do collaborate on a number of issues.

Mr. PORTER. Thank you, Dr. Olden.

Mrs. Lowey.

COST-BENEFIT REQUIREMENTS

Mrs. LOWEY. Thank you, Mr. Chairman.

Thank you very much for your testimony. In your statement, Dr. Olden, you make reference to NIEHS research that contributed to one of the greatest public health success stories in recent years, the tremendous drop in the levels of lead in our blood. Specifically, since the EPA began to phase down the levels of lead in gasoline and paint 25 years ago, we have seen a 76 percent decline in the mean lead blood levels in children. While no dollar figure can be easily assessed on the value of that decline, we know that countless children have been spared the subtle erosion of mental and psychological functions caused by elevated lead levels in people of all ages, particularly in children.

Had the risk assessment and cost-benefit requirements contained in legislation that recently passed the House been in effect in the mid-1970s, it is my understanding that the EPA's actions back then, which were vehemently opposed by the lead industry, would have been delayed significantly, perhaps by many years.

In reading from this report, I note that the NIEHS and NTP hosted a special workshop on January 11 through 13 and this was important to that dialogue, and it specifically says that recommendations from this workshop will provide a framework for developing risk assessment schemes and prevention programs that will enhance our ability to protect the public health from environmentally caused diseases while maintaining economic vitality.

Given that, would you please comment on the ramifications these new risk assessments and cost-benefit requirements will have on the work of NIEHS?

Dr. OLDEN. Well, the Administration has already articulated its position on that legislation. Let me say my concern is this, the science, to underscore, to underpin the decisions, is simply not in place to make the kind of decisions that I think need to be made. I am concerned about the quality of the science that goes into the regulatory decisions. And as I said earlier, in my opinion, in most cases, we have to make the decisions at a point where we have very little evidence to make those kinds of decisions.

I am concerned about birth defects, cancers, infant mortality, and not so much about cost benefits. I think those are value judgments that policymakers have to decide. But my concern is that we do not have good scientific bases for making decisions. For example, we do not understand differences in susceptibility. In most cases we do not know what the effects are at low doses. In most cases we are extrapolating from an animal to a human. These are the concerns that I have, not so much about cost benefits.

I think you as a policymaker must be concerned about those, but as the director of a health agency I am concerned about the quality of the decision and the quality of the science that goes into those decisions.

Mrs. LOWEY. I appreciate that, because it would seem to me that with the opposition to this work from the lead industry, I wonder, if this legislation had been in place, whether we would have been able to protect the public. The decisions we make, if this legislation goes through the other body, will not really be adequate because we will not have all the information we need. That is my real concern. I cannot help but believe, due to the pace at which this legislation went through, that many Members were not really thinking of the specifics, such as the lead implications and in a whole range of public health issues.

Dr. OLDEN. The costs for regulatory compliance as well as for health care costs are enormous, and it seems to me that it would be a wise policy to make the investment to do the science. And as soon as that could be done, with a fraction of the resources that it would take to enforce regulations that may or may not be required, we could rehabilitate or treat humans who have disabilities or diseases as a consequence of these exposures.

RISK ASSESSMENT

Mrs. LOWEY. So you share my concern that it may be very difficult to protect the public because hard data will not be available at the time decisions will have to be made?

Dr. OLDEN. Well, risk assessment is not an exact science, so in most cases we will never have all the data to eliminate all the uncertainties. However, I think with a different kind of orientation, the way we do the science, that we can have much of the data in hand when the decision must be made.

For example, it takes four to five years to complete a rodent carcinogenicity bioassay. It takes another year and a half or so to have that data peer reviewed and reported out. So we are talking anywhere from five to six years from beginning to end. During that time, one could conduct some limited epidemiological studies in human populations, so you would have that additional data. You could also do some mechanistic studies.

In other words, ask the question could this particular chemical alter a function in humans and you could do dose response studies in that period of time. And having mechanistic information would be very important in the risk assessment decision. So I think we can improve the database.

Mrs. LOWEY. Well, I thank you, and I do not know whether there have been any results published as a result of that dialogue as yet from the January 11 through 13 conference.

Dr. OLDEN. I don't think the report is out yet. The purpose of that conference was, as we develop the new technologies and methodologies, to convince regulatory agencies to use those new technologies and methodologies. And, secondly, regulatory agencies are, in many cases, constrained by legislation. The benchmark now for carcinogenicity and toxicity is carcinogenesis with the rodent bioassay, so they have the use of the rodent bioassay. So if we developed a different model that would be just as effective, they still have to get permission, authority, approval to use that, even if they wished to do that.

So we have to educate not only policymakers but we also have to educate and get buy in on the part of regulatory agencies. So that is why we had the three groups together at the conference in Research Triangle Park. And the report will be ready in May. So about two months from now.

Mrs. LOWEY. I appreciate that, because, as we know, the Senate operates on a different schedule. And when this bill is considered in greater detail, hopefully, through adequate hearings, there will be some thought given to the impact on public health. So I thank you.

BREAST CANCER GENE

Another question about the relationship between the discovery of the BRCA–1 gene for breast cancer and environmental factors. Could you discuss in greater detail how you believe the discovery of the gene for breast cancer and information on environmental causes of breast cancer are related? Does the discovery of the gene provide us any new information about environmental causes of breast cancer?

Dr. OLDEN. Not yet. Environmental agents fundamentally act two ways. They mutate or alter genes or they modulate gene function or they impair cellular signaling mechanisms. So we were interested in genes because we are interested in understanding how environmental agents interact with those genes, and BRCA–1 is just one example of genes that we are interested in. We are interested in other genes involved in other processes as well.

What we wanted to do was to isolate the gene and then create a transgenic animal. In other words, put that gene into a mouse and create an animal model of human breast cancer. Then we can expose those animals to various environmental agents including estrogens, which are at the top of our list, and ask do they in any way interact with that particular gene, or others, to increase the susceptibility of breast cancer, to increase the occurrence of breast cancer in an animal model system.

So by having the gene, it allows us to probe which environmental agents interact with genes and how they interact with genes; are they going to cause additional mutations or will they modulate at some other level.

Mrs. LOWEY. Well, thank you, Dr. Olden, and thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Bonilla.

SUPERFUND WORKER TRAINING PROGRAMS

Mr. BONILLA. Thank you, Chairman.

Hello, Dr. Olden, it is good to see you again.

Dr. OLDEN. How are you?

Mr. BONILLA. Fine, thank you. I would like to begin with a program that we have received some questions on that distributes grants through your Institute. You state in your testimony that the programs supported by NIEHS are consistent with the goal of prevention of human disease and disability, and aid in the formation of economic growth and the promotion of public-private partnerships.

I have a series of questions about a program that I think is not a promotion of public-private partnerships.

My first question is how much does NIEHS spend for grants for the training and education of workers who are or may be engaged in activities related to hazardous waste removal or containment or emergency response?

Dr. OLDEN. We spend, I believe, in the neighborhood of $20 million a year for support of our EPA Superfund Worker Training Program.

Mr. BONILLA. I had a figure that I thought was correct but perhaps it is not, of $37 million.

Dr. OLDEN. You are probably including training initiatives with DOE and other agencies. The EPA Worker Training Program is in the neighborhood of $20 million.

Mr. BONILLA. How many workers trained under the grants program under SARA are actually working or have worked in the hazardous waste field subsequent to attending the NIEHS grantee training program?

Dr. OLDEN. I think I am right in saying that all of them currently—they were employed in the hazardous waste industry before they took our training and they went back to their jobs. That was a requirement early on. Now we are creating a new program where that is not a requirement.

This year we were given $3 million to develop a similar program for low-income, young, unemployed inner-city workers, and that program is just getting started and I think we have not actually awarded a single grant yet, but that will happen soon.

But in the program you are referring to, all of the individuals are already employed in some industry and they come, they take our training and they go back to their previous job.

Mr. BONILLA. These workers you just referred to that are to be part of the program, you said inner-city workers?

Dr. OLDEN. Yes.

Mr. BONILLA. What qualifications would they have for participating in this program?

Dr. OLDEN. You have two things. First of all, they have to be supported—the individuals who apply for the grant have to demonstrate to us that they have or will have employment once the training is completed. Also, the individuals will have to be willing to take certain courses in mathematics, in arithmetic, for example, because one of the complaints that we hear is that many inner-city workers, low-income, unemployed, lack the skills for the highly skilled labor force. And when we train them, we want to be certain and the trainers want to be certain that these individuals are employable.

So not only do they have to take the training, it is a longer course than the other one, but they also have to attend a community college for a period of time. So it is a longer course. It could be one or two years. The other one is a matter of days or weeks. It could be a six weeks, eight weeks course. But these are individuals who are already employed so it is a different program.

We are trying to reach the unemployed and difficult to employ. It provides special skills.

RELATIONSHIP BETWEEN TRAINING AND WORK

Mr. BONILLA. What relationship, Doctor, if any, is there between the training being given under these grants and the work being done in the field?

Dr. OLDEN. Well, I am now insisting on a study to get that information. But the individuals I can say who have been trained are all employed. Now, whether they are being trained for jobs that exist today or whether they are being trained for jobs that exist in the future is, I think, the concern. But, clearly, none of the individuals that are trained are unemployed.

The environment is a growing industry, so there are a lot of jobs in the hazardous waste industry. Matter of fact, there are more jobs at the present time than there are people. So I do not think that is an issue, although I think we need to demonstrate that we are, indeed, training people for jobs that are going to be there for the next decade and beyond. But I think at the moment there is no doubt that we are doing that.

Mr. BONILLA. Do you have any mechanisms now in place that monitor the effectiveness of these programs?

Dr. OLDEN. Yes, we do. It was put in place at the beginning of the program in 1987, because as I indicated, we wanted to be certain that we are training people for jobs that do or will exist in the future. And so we have made it a requirement that all the grantees have to do an evaluation.

Mr. BONILLA. What involvement, if any, do the employers of hazardous waste workers have in this grant program or in the training and have they been involved at all in the course design or the actual training? The employers themselves.

Dr. OLDEN. The employers—well, the grants go to joint labor-management funds, universities, community colleges, and unions. The unions have been involved in the creation of the curriculum, but the employers, which would become a State or a county, no, they are not at all involved, to my knowledge, in the development of the curriculum.

Mr. BONILLA. We are getting near to the crux of what I am trying to get at and that is, does this involve the private sector or not or does it just involve your Institute and labor unions, and in my view it should. There is a circle here that is not completed if employers are not also participating in this program.

Dr. OLDEN. Well, some employers are sponsoring training courses at their plant sites—they are not involved in the design of the curriculum, but they are participating in the sense that they have said to us that this training is desirable and necessary. Because they pay. We do not pay for people to come. They come for weeks or days at the expense of their employer. We pay for the development of the curriculum. We pay for the trainer, the individuals who actually do the teaching. But these people are employed and on the payroll of their employers. So it is a partnership between the employer, our grantees, and the Institute.

Mr. BONILLA. I have a series of questions related to this, Doctor, but to accommodate this committee's time today, I will submit these for the record, if I could, and I would appreciate it if you would get back to me on that.

Dr. OLDEN. All right. I would be very pleased to do that.

Mr. BONILLA. Thank you.

Mr. PORTER. Thank you, Mr. Bonilla.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Olden, nice to see you again.

Dr. OLDEN. Thank you.

ASTHMA

Mr. STOKES. Dr. Olden, studies reveal that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. To what extent is research in this area covered in your Institute?

Dr. OLDEN. We are concerned about the environmental component of asthma, and we are cofunding, in fact, some of those inner-city projects that Dr. Fauci referred to. We are cofunding some projects with the Institute of Allergy and Infectious Diseases.

We are interested in three aspects. Asthma is a very high priority of our Institute. We have supported for a long time a number of studies called the Six City Study, the Twenty-four City Study, and the Five City Study to look at the health effects of air pollution. We focused on fiber toxicology; we focused on particles in the atmosphere, both large and small, and how they impair pulmonary function. We have looked at ozone, acid aerosols, and also nitrogen and sulfur dioxides.

Mr. STOKES. Are there any significant findings?

Dr. OLDEN. Well, it has been in the press. Matter of fact, I think in yesterday's paper, but certainly in the press in the last week or so a number of articles have appeared describing the work of one of our grantees, Doug Dockery, at Harvard Medical School, in which he found that people in the nation's most polluted cities are 15 to 17 percent more likely to die prematurely than those in cities with the cleanest air. Now, these are cities that meet clean air standards, but in those most polluted cities, there is an increased mortality, cardiovascular as well as pulmonary. That is due to small particles in air, not the ones that are regulated, which are the larger ones.

So, yes, there have been breakthroughs. The air is certainly getting cleaner, but we are spending more time indoors and it is probably indoor allergens, as Dr. Fauci pointed out, that are the problem. Our houses are tighter. We are using more synthetics in construction and that is probably part of the problem. So probably it is not only outdoor air.

LEAD POISONING

Mr. STOKES. Dr. Olden, what is the status of the treatment of lead poisoning in children clinical trial?

Dr. OLDEN. The treatment for kids who have clinical symptoms, that is who have blood lead levels in excess of 45 micrograms per deciliter of blood, is very good. There is no treatment at the present time for children who have blood lead levels below 40 micrograms per deciliter of blood.

When the treatment was developed many years ago for clinical lead poisoning, it was not known that low lead levels caused any effect. But now we know that lead levels all the way down to 10 micrograms per deciliter of blood cause neurological impairment, IQ neuromotor problems, and behavioral problems.

Now we are supporting, sponsoring, a multicenter clinical trial to develop a treatment for these low blood lead levels, and we are focusing on the range between 25 and 40 micrograms per deciliter of blood. And we are in the second year of a multicenter trial.

ENVIRONMENTALLY-RELATED DISEASES IN CHILDREN

Mr. STOKES. What other significant research is underway at your Institute to address environmental-related diseases in children?

Dr. OLDEN. Well, we are very interested in susceptibility. We are interested in susceptibility to pesticides. We are interested in which environmental agents influence developmental genes. And we have a study that is ongoing to look at both.

We have, in fact, just recently awarded six grants to look at environmental agents that influence the genes that are known to be involved in development. We initiated a NTP study to look at both pre- and post-natal development following exposure to different pesticides.

Mr. STOKES. Thank you, Dr. Olden. Thank you, Mr. Chairman.

FACILITY CONSTRUCTION

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Olden, last year you testified that $10 million would be needed in 1995 and $23 million in 1996 to complete construction of your lab and office space complex at the Research Triangle Park in North Carolina. Although you received the $10 million in 1995, the Administration requests only $6 million in 1996 instead of $23 million. Does that represent a slowdown in construction or are you rethinking the scope of the project? If the Administration's funding requests are approved, how long would it take to finish?

Dr. OLDEN. We made a decision not to build. There were two parts to the construction. There was a laboratory unit and an office. And we made the decision not to construct the office portion. So we have enough money in hand, with the exception of the $6 million requested and that is for the utilities. So the money for the construction of the facility is in hand. We simply need the $6 million to put the utilities into this building.

PARKINSON'S DISEASE

Mr. PORTER. Your Institute is scheduling a workshop on the link between environmental toxins and Parkinson's Disease. What implications does the exploration of this Parkinson's toxic link have for other neurological disorders?

Dr. OLDEN. Well, there is some evidence to suggest that Parkinson's is caused by exposure to heavy metals, zinc, manganese, and mercury. We have, for a number of years, had substantial research programs not only in lead but also looking at mercury toxicity and zinc. And so what we want to do is bring together a group of experts and explore what is known, more about the role of zinc and mercury. This is what we are going to focus on. We want to know what is the state of the science and is there sufficient evidence to suggest their involvement so that we can get the scientific community involved or to define a research agenda for those two metals.

ELECTROMAGNETIC FIELDS

Mr. PORTER. Last year we discussed the possibility of health effects of electromagnetic fields.

Dr. OLDEN. Yes.

Mr. PORTER. It sounded then as if the jury was still out. Have any more findings been released in the past year that can more definitively answer this question?

Dr. OLDEN. Mr. Chairman, it is a five-year study and last year we were in year one. This is, obviously, year two. We do not know the answer yet, but I was told this morning, as I rode up on the plane with my colleague who is in charge of this, that I will have the data in 1997, which is when I am supposed to have it.

Let me say we do know some things. This is an area that has been explored primarily by physical scientists prior to our involvement. There are some epidemiological studies to demonstrate there are weak associations between exposure to EMF and certain cancers, leukemias, for example.

However, there is simply no biological explanation for why EMF should cause cancer or any disease or dysfunction. So what we wanted to do, first of all, was controlled laboratory studies in animals to develop the biological basis for plausibility. One of the hypotheses was that a hormone called melatonin was depressed by exposure to EMF and that this allowed for proliferation of the cancer cells that had already been initiated.

In the animal studies—they may be behaving differently from humans—to date we see no evidence that EMF is altering in any way melatonin production, as assayed by the amount of melatonin in the blood. The biological plausibility has been not been established yet, but it is a new program.

Mr. PORTER. Melatonin is produced by the pituitary gland; is that right?

Dr. OLDEN. Pineal.

Mr. PORTER. Pineal. I will get these things after a while.

Let me ask the Members of my subcommittee whether they have additional questions. Mr. Stokes? Mrs. Lowey?

ENVIRONMENTAL INJUSTICE

Mr. STOKES. I have one additional question I would like to pose, Mr. Chairman, if you don't mind, and then I will submit the others for the record.

Mr. PORTER. All right.

Mr. STOKES. Dr. Olden, as environmental mandates are being relaxed, what are the implications for increased environmental-related disease and increased environmental injustice? That is, what are the environmental-related diseases that would be most threatening to the health of the American people and specifically to our children that could result?

Dr. OLDEN. Well, Mr. Stokes, that is difficult to answer. I tried to point out earlier that we do not understand how children differ from adults in terms of susceptibility. We regulate now as if all of us are 170 pound males and that is simply not true. I heard the other day that someone said we regulate us as if everyone is an Arnold Schwarzenegger, so that is not correct.

Children are different from adults biologically, and we have lots of evidence that they are more susceptible. For example, in the lead studies, adults are exposed to lead also, but the critical time period is from conception to age six years old. That is also the issue with pesticides. Children's eating habits are different. They consume more water. So if there are pollutants, toxins in water, pesticides in foods, children may be affected more.

So it is clear that children, senior citizens, and socioeconomically disadvantaged people are probably the victims of what is typically known as environmental injustice. Children, because we simply ignore them—we look over their heads in regulation. Poor people, because they live and work in the most hazardous environments. In the case of senior citizens, their immune systems are suppressed, and we measure for healthy adults. So if regulatory standards are relaxed, clearly the individuals that will be affected first are the same groups that are at higher risk presently: children, the poor, and senior citizens.

Mr. STOKES. Would you subscribe to the fact that there is such a thing as environmental injustice?

Dr. OLDEN. Well, it is clear that poor people have more morbidity and mortality. And they suffer from diseases that are preventable. It is true, well-established, that they live in the most hazardous environments, they work in the most hazardous occupations, and if you believe, as I do, that these environmental agents that we demonstrate are carcinogens or cause birth defects or cause pulmonary dysfunctions, then if you believe that they cause diseases in humans, then I think that some of the morbidity, excessive morbidity and mortality of these groups must be related to where they live, where they work, or the fact that they are children or the fact that they are senior citizens.

Yes, I do. I think there is great evidence of that.

Mr. STOKES. Thank you, Dr. Olden. Mr. Chairman, I will submit the balance of my questions for the record.

Mr. PORTER. Thank you, Mr. Stokes.

Mrs. Lowey.

LONG ISLAND BREAST CANCER STUDY

Mrs. LOWEY. Thank you very much, and I appreciate again the testimony. And I wonder if there is an update that you can share with us on the Long Island breast cancer study. I know this is a joint study between your Institute and NCI and if there is any information you can share, Dr. Olden, I would be appreciative.

Dr. OLDEN. I will have to submit that. I know we are conducting a case controlled study that is cofunded with the National Cancer Institute as part of the Long Island breast project, but I am sorry I cannot give you an update on that.

[The information follows:]

LONG ISLAND BREAST CANCER STUDY PROJECT

The Long Island Breast Cancer Study Project (LIBCSP) will evaluate the contribution of various environmental and occupational factors to the etiology of breast cancer. Over the five-year project period, the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences will spend about $15 million ($4 million in FY1995) to look at the effects of exposures to contaminated drinking water, sources of indoor and ambient air pollution, electromagnetic fields, pesticides and other toxic chemicals, and hazardous and municipal waste. The research is supported through grants and cooperative agreements to universities and biomedical research institutions, and through interagency agreements. The use of state-of-the-art technology to complete this study is being emphasized.

Core Research Component

The core component of the LIBCSP is a grant to Columbia University and a consortium of NCI cancer centers and New York hospitals for a case-control study. This population-based study potentially will enroll every woman diagnosed with breast cancer (approximately 1,600 women and matching controls) on Long Island during a one-year period, and gather exhaustive environmental information. ($6-8 million total)

Other LIBCSP Studies:

- Scientists at The American Health Foundation are enrolling women for a study of pesticides and breast cancer. ($1-2 million total)
- Epidemiologists at the Brookhaven National Laboratory are identifying data sources on environmental factors and developing a geographic information system. This computer-based technology will integrate data on water, air and soil contaminants, toxic releases and other factors, with locations in space and time. The Environmental Protection Agency is cooperating with this effort. ($2 million total)
- Another study at SUNY-Stony Brook will investigate reducing barriers to the use of breast cancer screening. ($1.5 million total)
- Pilot studies to assess biologic markers for environmental exposures have been funded at several New York area cancer centers. ($1 million total)
- NCI epidemiologists abstracted cases from the New York State Tumor Registry to estimate its accuracy and to offer expert assistance. ($100,000 total)

Ad Hoc Advisory Group:

- The Group is comprised of 10 scientists, 4 community advocates, and 2 ex-officio community members, and will meet several times a year as needed. The first meeting was held in March 1995.

Community Liaison:

- NCI LIBCSP staff have met regularly with breast cancer advocates. Interactions with the community have been arranged with community representatives.
- Two open meetings (February 1994 and March 1995) have been held on Long Island.
- A meeting with Columbia University was held in January 1995 with the Long Island Breast Cancer Network, followed by a public announcement of the grant.
- Regular updates on the LIBCSP have been provided to the Congress, the advocates, and the press.

Mrs. LOWEY. Thank you.

Dr. VARMUS. I recommend you ask that, Mrs. Lowey, to Ed Sondik when he appears here tomorrow.

Mrs. LOWEY. Thank you very much. Thank you, Mr. Chairman.

CLOSING REMARKS

Mr. PORTER. Thank you, Mrs. Lowey.

Dr. Olden, we appreciate very much your good testimony today and thank you for the fine job that you are doing. This concludes the program for today. We will recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

CLEARINGHOUSE

Mr. Porter: What is the budget for your toll-free clearinghouse in 1995 and 1996, and how many calls are projected to be received?

Dr. Olden: The NIEHS clearinghouse, known as ENVIROHEALTH, has a budget of $457,567 for FY 1995 and $515,928 for FY 1996. We are currently receiving calls at the rate of approximately 5,000 inquiries per year. However, the number of calls is increasing and is expected to be dramatically higher in response to our publicizing the availability of the clearinghouse.

The goal of our clearinghouse is to provide interested parties with free information on environmental health and how NIEHS research efforts relate to their areas of interest. One function of ENVIROHEALTH that has grown rapidly is its referral service. Callers dial this one number to get referrals on questions when they might otherwise have to contact their primary physician or local, state, or federal agencies before they found the appropriate information service for their question. Thus, ENVIROHEALTH saves the callers and responders time, trouble, and money.

SUPERFUND

Mr. Porter: Provide a five-year table of funds received from Superfund, broken down into research and worker training.

Dr. Olden: The following table provides a five-year history of funds received by NIEHS from EPA for carrying out our Superfund responsibilities:

NIEHS
SUPERFUND
(Dollars in Thousands)

	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995 Estimate
Basic Research and Professional Training	$21,915	$30,640	$31,915	$32,915	$35,775
Worker Safety Training	20,000	20,000	20,125	20,000	22,943
Total	41,915	51,140	52,040	52,915	58,718

NATIONAL TOXICOLOGY PROGRAM

Mr. Porter: Identify 1994-1996 funding for the National Toxicology Program from all agency sources.

Dr. Olden: The following chart shows the 1994-1996 funding for the National Toxicology Program:

CONTRIBUTIONS TO NTP BY AGENCY
(Dollars in thousands)

	1994 Actual	1995 Estimate	1996 Estimate
NIEHS	$76,600	$83,000	$87,270
NCTR	510	557	660
NIOSH	5,288	4,937	5,250
Total	82,398	88,494	93,180

USE OF MAMMALS IN TESTING

Mr. Porter: Have you seen any progress during your tenure at the Institute in decreasing the use of mammals in chemical testing?

Dr. Olden: During my tenure at the NIEHS, excellent progress has been made in the development of testing methods that will decrease the use of mammals in testing. The NIEHS is developing mechanistically-based alternative methods and models for toxicology research and testing that utilize non-mammalian species, non-animal methods, and other strategies that may reduce the number of mammals required. These methods incorporate recent advances in our understanding of the molecular mechanisms by which chemicals exert their toxic effects. Improved test methods are sought that are more predictive of the potential human health hazard and that will provide information more supportive of quantitative human health risk assessment. Such methods may also be more cost-effective and achievable in a shorter time frame than current methods. Integrating these alternative non-mammalian and non-animal methods into testing strategies will facilitate more efficient animal use by identifying chemicals with the highest priority for further evaluation. The degree to which our future reliance on mammals for toxicity testing will be decreased will depend largely on the resources that are devoted to develop and validate non-mammalian and non-animal testing methods. However, singly or in combination, these alternative assays cannot approximate the complexity of interactions that take place in a living mammal. Thus, for the foreseeable future, non-mammalian and non-animal methods, such as invertebrates, fish, computer modeling, and cell systems generally will be used in conjunction with laboratory animal models. Where it is necessary to use any animal species, the Institute will continue to seek refinements to optimize animal well-being and to pursue strategies that will further reduce the number of animals required. So although animal use can now be reduced somewhat by these new approaches, continued animal use is essential for the time being.

Mr. Porter: Are extramural researchers reluctant to undertake toxicological testing because of harassment from animal rights groups?

Dr. Olden: NIEHS extramural researchers have been able to continue their toxicological research and testing unimpeded by animal rights groups. Nonetheless, they are cognizant of the harassment of scientists conducting other types of biomedical research. Extramural researchers generate information that is used to support risk assessments conducted primarily to protect human health. It is also important to recognize that animals represent only one of many important model systems used in toxicological research and testing. Other models include mathematical and computer modeling, microorganisms, cell and tissue cultures, clinical observations, epidemiology, and a variety of other approaches. Modern toxicological research and testing depends on the integrated use of a combination of these models and methods in a complementary and interactive manner. Animal welfare organizations have been supportive of our efforts to develop new and revised testing methods that result in the reduction of animal use, that incorporate refinements that further enhance animal well-being, and that provide for the partial or total replacement of animals with non-animal systems or a phylogenetically lower species.

Mr. Porter: Have you had any difficulties in this regard at your intramural lab facilities?

Dr. Olden: No, we have not experienced this type of problem at our intramural lab facilities.

CLINICAL RESEARCH

Mr. Porter: Last year, you testified about initiating a clinical research component. Is that effort now underway? Can you describe the types of clinical research you anticipate funding, and at what level?

Dr. Olden: NIEHS awarded two contracts for support of clinical research to Duke University and the University of North Carolina in 1993. We have a training program in place in which physicians and nurses spend one year in the clinical setting, learning how to do clinical research, and another year in the lab at NIEHS, learning the basic or applied science aspect of environmental science. Studies to date have involved the problem of severe childhood anemia in sub-Saharan Africa, and the genetic changes in cancer susceptibility genes that occur in environmentally induced lung cancer. Future plans include work on the relationship between paternal occupation and birth outcome, such as birth defects and low birthweight, and on the relationship between bone density in older women and their exposure to the pesticide DDT, which may act as an "environmental estrogen". The core administrative support of the program and associated trainee cost are about $845,000 per year.

STREAMLINING

Mr. Porter: You have recently reorganized your Institute to streamline and shift priorities. Yet, there do not appear to be any significant personnel reductions from 1994 to 1996. Why is that?

Dr. Olden: In 1993 the Institute used 750 FTEs. We reorganized that year and combined three intramural programs into one with the intent of reassigning resources to those areas we wished to emphasize. While we were in the midst of that redirection, we were placed under a freeze and did not replace employees who left; thereby, making our FY 1994 on-board count lower than our ceiling of 733. Our actual reduction has been 49 FTEs over that period. We have also reduced our number of senior level employees from 105 to 95. We will continue to reduce our total number of personnel while we continue to reassign remaining employees to the areas of highest priority.

TRAINING CRITERIA HAZARDOUS WASTE OPERATIONS AND EMERGENCY RESPONSE

Mr. Bonilla: What involvement, if any did the employers of hazardous waste workers have in the development of the minimum criteria for training which OSHA eventually published in the **Federal Register** as Appendix E? If not, why not?

Dr. Olden: Employer representatives, invited on the basis of their expertise in occupational safety and health, participated along with representatives from labor, academia and other federal agencies in a tri-partite 1990 technical workshop that developed minimum criteria for hazardous waste operations and emergency response and in a tri-partite 1994 technical workshop that developed interpretative guidance to the minimum criteria for hazardous waste operations and emergency response.

These minimum criteria were developed in the absence of any other guidance in this area to help NIEHS, in its management of this program, to assure high quality of worker health and safety training. High quality worker training is important to help hazardous waste workers and emergency responders at highest risk of injury and illness to protect themselves and is consistent with the statutory authority of NIEHS to develop model programs.

Mr. Bonilla: Why does NIEHS believe it is in within its charter or responsibility to develop or recommend minimum criteria for this training which exceed OSHA's requirements?

Dr. Olden: NIEHS is responsible for the stewardship of this federal assistance program for model worker health and safety training programs authorized under Section 126 of the Superfund Amendments and Reauthorization Act of 1986 (SARA). NIEHS convened the series of workshops to develop minimum criteria in the absence of any other guidance in this area for the purpose of better managing the program. Since then OSHA has adopted certain parts of the minimum guidance in non-mandatory Appendix E of 29 CFR 1910.120, Hazardous Waste Operations and Emergency Response (HAZWOPER).

Mr. Bonilla: Is there any documentary evidence that provision of accredited training results in safer employee behavior or fewer employee injuries and illnesses?

Dr. Olden: NIEHS awardees participating under this program have continually evaluated their training efforts, including post-training follow-up with trainees. One of many examples of the impact of training effectiveness of the NIEHS-supported program may be seen in the peer-reviewed Journal of Occupational Medicine (McQuiston, T., et.al., Hazardous Waste Worker Education - Long Term Effects, Journal of Occupational Medicine, Volume 36, Number 12, December 1994.) This longitudinal post-training study or a 12 month follow up of 481 trained workers and 50 management trainees found training material to continue to be used by more than 70 per cent of respondents; co-workers were taught about safer work practice by more than 70 per cent of respondents; 50 per cent of workers went on to train their management in safer workplace conditions; and more than 90 per cent identified problems at work and sought, and obtained, changes in programs, training or equipment to make their workplaces safer. Managers substantially supported worker reports in this study.

Other evaluation studies of this training show a significant improvement in the appropriate post-training use of personal protection on the job; improvement in health and safety response knowledge, and a significant increase in awareness of workplace hazards.

Mr. Bonilla: If the emphasis in the NIEHS training grants is to ensure that employees are trained, and as grantees have developed the training programs with government funds, why are the training materials not being offered to employers for only the cost of their duplication? Have employers been provided or offered this opportunity to have training conducted on their plant sites for the minimal cost of trainer travel expenses and duplication of materials?

Dr. Olden: Curriculum material is available to the public at the cost of reproduction from the NIEHS sponsored National Clearinghouse for worker training. The clearinghouse also publishes a newsletter, assists with technical workshop organization, and provides information on hazardous waste worker and emergency responder-related training issues.

Since the initiation of the NIEHS-administered Superfund Worker Training Program in 1987, over 20,000 courses have been held in conjunction with numerous employers at hundreds of plant sites in dozens of construction and industrial settings. Joint labor-management training funds, community colleges, unions, universities and public health organizations, who have been supported with federal tax dollars, have all striven to assure worker and employer input and involvement in all stages of the training process--from curricula development though training delivery and program evaluation. Costs of travel and duplication of materials have been minimized at each step in the process.

ACCREDITATION OF TRAINING

Mr. Bonilla: What is the utility of accrediting a course whose requirements are so general that they must be, and are required to be, supplemented by site-specific information and on-site experience before an employee is considered trained in accordance with the statue?

Dr. Olden: NIEHS does not accredit courses. NIEHS requires its worker training awardees to follow the minimum criteria for worker health and safety training for hazardous waste operations and emergency response to assure a high standard of quality training. The minimum criteria provide a basis of assessing training quality and follow the OSHA standard for hazardous waste operation and emergency response. The minimum criteria, developed through participation of experts in occupational safety and health, and published in the peer-reviewed literature for comment are a professional technical guide for quality worker training. These criteria have been enhanced with interpretive guidance developed in an NIEHS-sponsored technical workshop.

MINORITY WORKERS

Mr. Bonilla: How many minority workers trained under the SARA grant program are actually working in hazardous waste operations trade?

Dr. Olden: NIEHS and its grantees have gathered evidence that minority workers who are trained in the program are in fact employed in hazardous materials-related activities. For instance, in the case of Laborers-Associated General Contractors, outreach over the past few years to Native American communities has allowed for training for more than 15 different tribes. The California-Arizona Consortium has been in the forefront of minority training since 1987 by developing curriculum in Spanish, providing 14 courses in Spanish for Latino workers in the Southwest, and reaching more than 300 minority workers each year.

Mr. Bonilla: What relationship, if any, is there between the training being given under these grants and minority candidate work being done in this field?

Dr. Olden: According to reports of minority group participation for each grantee during the past year, approximately 25% of all trainees identified themselves as members of minority groups. Given the national workforce in hazardous waste operations, this percentage is a reasonable reflection of the target population for hazardous waste training.

ACCREDITATION OF TRAINING

Mr. Bonilla: Since OSHA does not require accreditation for any of the other training it regulates, why does NIEHS believe that OSHA should require accreditation in this instance?

Dr. Olden: NIEHS must assure that model worker health and safety training programs provide a high level of training quality and has developed minimum criteria for these purposes. Training program accreditation is another means to achieve training quality, much as universities and colleges rely on accreditation for quality assurance.

OSHA is required to establish an accreditation program by statute for the purposes of assuring training quality. This is consistent with other areas of environmental clean-up such as asbestos and lead-based paint abatement which also require accreditation of worker training programs. NIEHS has supported OSHA's efforts to carry out the Congressionally-mandated rulemaking on accreditation to assure high quality safety and health training programs for hazardous waste workers in high risk occupations.

Mr. Bonilla: OSHA has established the legal requirements for training emergency responders in the Hazardous Waste Operations and Emergency Response Standard. If the employer is complying with the training requirements, what does accreditation add, in terms of increased employee safety and health, to justify the additional expense and burden on resources?

Dr. Olden: Establishing a federal accreditation process for worker safety and health training programs can be an important mechanism for assuring that workers in high-risk occupations receive comprehensive, technically accurate training from competent, well qualified training providers. The cornerstone for assuring an effective accreditation procedure for worker safety and health training is clear and uniform criteria for matching required training topics and modules with the job responsibilities and work tasks that trainees are expected to complete.

Mr. Bonilla: If an employer is not complying with the training requirements of the HAZWOPER standard--in essence violating the law--will the proposed accreditation requirements make the employer more likely to provide the required training? Please explain why.

Dr. Olden: Evaluation of NIEHS-supported model worker training programs show positive correlations with health and safety improvements in the workplace. Accreditation provides a basis for employers and other training providers to determine the appropriate requirements of a training program and to commit to a high level of quality control and responsibility. NIEHS would expect that most employers would follow the rules under which they were accredited.

EVALUATION OF TRAINING

Mr. Bonilla: Isn't the proof of the worth of any training program demonstrated by appropriate employee action or behavior on the job? Isn't the final determiner of whether safe behavior is being demonstrated by the employed be the compliance officer? Therefore, isn't the best deterrent to poor employer performance in providing adequate training a well-informed compliance officer?

Dr. Olden: NIEHS Worker Training grantees have been involved with training many compliance inspectors at both the state and federal levels for both occupational safety and health inspections and environmental protection compliance checks. NIEHS agrees that well-informed compliance officers are the best determiners of whether employers and employees are demonstrating safe behavior as a result of training.

ACCREDITATION OF TRAINING

Mr. Bonilla: OSHA has neither proposed nor adopted training accreditation requirements in any of its other safety and health standards. Why does NIEHS believe that OSHA should require accreditation in this particular instance?

Dr. Olden: Congress has required OSHA to develop an accreditation standard for 29 CFR 1910.120. NIEHS, based on evidence in the peer-reviewed literature and on evaluation of NIEHS-sponsored worker training programs, has found that high quality worker training correlates positively with health and safety improvements in the workplace. Accreditation to assure training program consistence at a minimum level is one means to achieve this.

Mr. Bonilla: The HAZWOPER standard has been in effect for a number of years without the requirement to provide accredited training. What documented evidence exists that training provided by employers to date has been inadequate to protect the workers of employers who are under OSHA jurisdiction?

Dr. Olden: OSHA compliance data show that the training rules are among the most often violated sections of this standard. From the promulgation of the interim 1910.120 standard in August 1987 (52 FR 29620) through the completion of the final rule in 1990, OSHA inspected over 600 workplaces in 41 states covering almost a quarter of a million workers in numerous industry settings. Violations of the OSHA HAZWOPER training requirements during these inspections were the second most frequently cited violation in an examination of these 600 inspections conducted by OSHA. A more recent summary of HAZWOPER citations compiled by the OSHA Office of Health Compliance Assistance found that citations for inadequate or non-existent training were the most common citation during Fiscal Year 1991 and the second most frequent citation during FY 1992, which is the most recently available data.

TRAINING AND EMPLOYMENT

Mr. Bonilla: What has NIEHS done to ensure that program grantees have, in fact, trained employees who either were actually engaged or were to be engaged in these activities?

Dr. Olden: NIEHS has gathered evidence from its grantees indicating that workers who are trained in the program are in fact employed in hazardous materials-related activities. For instance, in the case of ironworkers trained under the program well over 70 percent are directly employed in hazardous waste remediation.

Mr. Bonilla: What data had NIEHS collected to show how many of the personnel trained actually used the extensive training they received versus how much of the training was not pertinent to the operations they were to be or became involved in?

Dr. Olden: All the information we have received to date from grantees and trainees have indicated that the training is extremely beneficial. Further studies are being initiated to confirm the usefulness of the training.

DEVELOPMENT OF CRITERIA

Mr. Bonilla: When NIEHS was in the process of developing the minimum criteria for training which eventually became Appendix E to OSHA's HAZWOPER standard, why were industry groups not actively solicited for input and not even somewhat equally represented at the meeting where the criteria were supposedly developed?

Dr. Olden: Employer representatives, including the Hazardous Waste Management Association, were invited on the basis of their expertise in occupational safety and health and participated along with representatives from labor, academia and other federal agencies in technical workshops that developed minimum criteria for hazardous waste operations and emergency response and a companion guidance document. In each case participants were invited based on several factors including publication in peer-reviewed journals, active involvement in professional occupational health and safety societies and suggestions from peers in the field of worker health and safety training.

ACCREDITATION FOR EMERGENCY RESPONDERS

Mr. Bonilla: If NIEHS' primary mission is research, why does NIEHS believe it is within your responsibility or charter to support organized Labor's lobbying of OSHA to extend accreditation requirements to emergency responders under OSHA jurisdiction?

Dr. Olden: NIEHS has no involvement in lobbying and only provides technical comments to OSHA through the standard rulemaking process. Moreover, no federal funds may be used for lobbying by NIEHS grantees, according to HHS and NIH policies.

BIRTH DEFECTS

Mr. Dickey: I have become increasingly concerned with the incidence of birth defects caused by some environmental component, such as cigarette smoke or gasoline fumes. What advances has NIEHS made in the area of environmentally-caused birth defects?

Dr. Olden: Many researchers have looked for environmental causes of birth defects but so far, not much evidence has turned up. This has led some scientists to conclude that environmental factors may not be as important in causing birth defects as has been thought. However, using data from a unique Norwegian registry, investigators showed that couples who have one child with a birth defect will have a lower risk of defect in their next child if they move to a different city. The argument is not that specific cities cause birth defects, but that couples who change residence also change many aspects of their environment. A major reduction in risk associated with moving must mean that environmental factors play a role in birth defects.

One reason researchers have had trouble finding environmental causes of birth defects is that environmental hazards may effect only certain subgroups of the population who are genetically susceptible. Epidemiologists at NIEHS are pursing this in a cleft lip study that includes both genetic and environmental factors. This study is the largest of its kind, incorporating newly-developed methods of molecular biology in a large population-based study. Enrollment of cases will begin this summer and run for five years.

Mr. Dickey: What mechanisms are in place to give pregnant women the information they need to avoid environmental components that are thought to cause birth defects?

Dr. Olden: NIEHS has used every possible avenue to disseminate information from our research that indicates that a substance may be associated with birth defects. We formally notify the Food and Drug Administration, the Agency for Toxic Substances and Disease Registry, the National Institute for Occupational Safety and Health, and the Environmental Protection Agency of the findings of our toxicologic research immediately upon completion of the peer review of the study findings. In those instances where preliminary research data indicate that an environmental factor may cause birth defects we alert these agencies so that they can begin the process of identifying women who may be exposed. In addition, we publish our research findings in scientific and medical journals to alert family physicians and other health care providers. Last year, I established an Environmental Health Information Clearinghouse at NIEHS where members of the public can receive. Information on birth defects risks from over 200 sources through a single toll-free phone number.

AIDS RESEARCH

Mr. Dickey: Is there any area of HIV and AIDS research that falls under the purview of NIEHS and if so, what are some of the advances made by NIEHS regarding an environmental cause of HIV or AIDS?

Dr. Olden: We have ongoing research on toxicology of HIV and AIDS therapies in animal models because we have extensive experience and expertise in reproductive, developmental and specific organ toxicity and carcinogenicity of chemicals under the National Toxicology Program.

We are also performing extensive research to understand why the HIV-1 has such a high mutation rate, since this high rate leads to rapid accumulation of drug resistant viruses within patients. Our scientists have identified the most likely cause of this high mutation rate and are now trying to understand how this process works. Such information could potentially lead to the design of a more effective drug that the virus cannot escape.

ELECTROMAGNETIC FIELDS

Mr. Dickey: What advancements have been made in the past year in your animal studies regarding prolonged exposure to electromagnetic fields?

Dr. Olden: The preliminary findings from our toxicologic study are currently undergoing peer review. We will report these findings at the meeting of the Bio-Electric Magnetics Society in Boston in June. I cannot give you a detailed report at this time but I have reviewed this information and we are not finding any health effects in these animal studies that would give rise to concerns about adverse effects in pregnant women or their babies which has been one of the major worries in this area.

Mr. Dickey: What have your studies of electromagnetic fields concluded regarding the use of advanced telecommunication and computing devices, such as cellular phones and personal desk-top computers?

Dr. Olden: NIEHS is not conducting any research directly related to possible health effects from these exposures. Congress specified that our research involve the magnetic fields produced by the transmission and use of electrical current in the 60 hertz frequency range. However we are consulting with the National Institute of Occupational Safety and Health. They have not found any significant health effects from exposure to video display terminals in the work place in their study. The National Cancer Institute is conducting a very large epidemiologic study of risk factors in brain cancer and has included research into the effects of cellular phones in this study. The results of their study are several years away.

LEAD CLINICAL TRIAL

Mr. Dickey: How is the "Lead in Children" Clinical Trial progressing?

Dr. Olden: The recruitment phase of the clinical trial, which we call the Treatment of Lead-exposed Children, or TLC, Trial, has been underway since late last summer, and as of March 20, 1995, 102 children had begun treatment. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home cleanup, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We hope to enroll a total of 1,300 children from Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years.

ASTHMA

Mr. Stokes: Asthma continues to be a major medical problem effecting 10 million Americans, more than one-third of whom are under 18 years of age. Studies reveal that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. To what extent are researchers supported by your Institute conducting research in this area?

Dr. Olden: The National Institute of Environmental Health Sciences (NIEHS) has a historical commitment to studying the basic scientific relationships between air pollutants and lung dysfunction and disease. We have joined with the National Institute of Allergy and Infectious Diseases (NIAID) in the National Cooperative Inner-City Asthma Study. The goal of this study is to design and evaluate asthma intervention strategies in underserved, inner-city children from 4 to 12 years of age. The NIEHS is focussing its efforts in this study on the environmental components of the intervention plan. If this intervention study is scientifically successful, the NIEHS will be in a strong position to develop a focussed program initiative directed toward understanding the mechanisms involved in the etiology of respiratory dysfunction from exposure to indoor environmental agents. A recent Program Announcement issued jointly by the NIEHS, NIAID and the National Heart Lung and Blood Institute will stimulate research to understand the mechanisms by which air pollutants exacerbate and contribute to asthma morbidity and mortality.

Mr. Stokes: What have we learned about the environmental factors associated with asthma since you were here last?

Dr. Olden: We have a rich abundance of positive data to link exposure to environmental agents, such as ozone, sulfur dioxide, particulates and acid aerosols, to increases in the prevalence of respiratory symptoms in children and adults. These studies have revealed that asthma appears to be exacerbated in those children with preexisting conditions, such as clinically diagnosed asthma, following exposure to outdoor air pollution. The indoor environment has also been a recent focus of interest, especially as individuals spend most of their life indoors. Elements in the indoor environment have been associated with asthma, such as house dust mites, cockroach, cat dander, tobacco smoke and nitrogen dioxide.

LEAD POISONING

Mr. Stokes: What is the status of the "Treatment of Lead Poisoning in Children" clinical trial?

Dr. Olden: The recruitment phase of the clinical trial, which we call the Treatment of Lead-exposed Children, or TLC, Trial, has been underway since late last summer, and as of March 20, 1995, 102 children had begun treatment. Study procedures have been very acceptable to the families involved, but recruitment has been slower than we had anticipated. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home cleanup, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We still hope to enroll about 1,300 children from Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years. We are now planning to extend enrollment to September 1996.

Mr. Stokes: What other significant research is underway at your Institute to address environmental related diseases in children?

Dr. Olden: Children may be more vulnerable than adults to environmental toxicants. At NIEHS, we are particularly interested in the effects on the child's nervous system. Inorganic mercury is a well-known neurotoxin in animal studies that has not been studied in children. We are collaborating with British scientists in a study of infants and children whose mothers received dental fillings late in pregnancy. Dental fillings contain mercury, which easily crosses the placenta. We will look at motor and cognitive development in these children.

Besides metals, other groups with very widespread exposures, from which children are at especially high risk, are the kinds of persistent pesticides and industrial chemicals that contaminate human breast milk, like DDT and PCBs. For many years now NIEHS has investigated the consequences of these exposures for children. In the U.S., we have shown that about five percent of women who have had no special exposure to PCBs transmit enough of the chemical already present in their bodies to their unborn child that we can detect subtle slowing of the child's motor development up until about age 2 years. In Taiwan, where women were poisoned by a very toxic mixture of heat-degraded PCBs, we showed that children had birth defects, developmental delays, and behavioral disorders even if they were born as long as seven years after their mothers' exposures had stopped. We have also looked for an effect on lactation itself of these kinds of chemicals, and have found that women with higher DDT exposures do not lactate as long, perhaps because DDT is an "environmental estrogen." Breast feeding is important for the optimal development of the child in this country, but in the developing world the success of breast feeding can determine whether an infant lives or dies.

Pesticides besides DDT may damage the nervous system. We are developing a U.S. study of the effects of pesticides on childhood development, with special interest in attention deficit/hyperactivity disorder (ADHD), the most common behavioral disorder seen in children.

Researchers from NIEHS are also working in Ukraine to study the effects of environmental toxicants on 2,000 mothers and their infants. As in other areas of the former Soviet Union, Ukraine suffers from accumulated environmental abuse, with years of unregulated use of pesticides and severe industrial pollution of air and water. We have carried out a study of infant survival. If it is scientifically feasible, we will continue with a study of childhood development.

RESEARCH PROJECT GRANTS

Mr. Stokes: Currently, what is the total number of research project grants funded by your Institute?

Dr. Olden: For FY 1995, the total number of research project grants (RPGs) funded by NIEHS is 417.

Mr. Stokes: How does this compare to the number funded in FY 1994 and the proposed number for FY 1996?

Dr. Olden: The number proposed for FY 1996 is estimated as 432 and the number funded during FY 1994 was 421.

Mr. Stokes: What is the success rate for each of these years?

Dr. Olden: The NIEHS success rates for FY 1994, FY 1995 and FY 1996 are 25.5 percent, 16.7 percent and 21.9 percent, respectively.

Mr. Stokes: For the NIH as a whole, the number of research project grants awarded appears to be remaining fairly constant. Is this trend true for your Institute as well?

Dr. Olden: The total number of RPGs for NIEHS has increased modestly from FY 1991 through FY 1994; however, the number of competitive awards has not kept pace with the increase in applications received.

Mr. Stokes: If we look at five year increments, what has happened to your Institute's success rate over the past five to ten to fifteen years. Explain.

Dr. Olden: There has been a decline in the overall success rate for NIEHS RPGs. The success rate for FY 1996 is projected at 21.9 percent, the success rate for FY 1991 was 27.5 percent, the success rate for FY 1986 was 25.7 percent and the success rate for FY 1981 was 36.6 percent. Accordingly, projections for success rates over the past five, ten and fifteen year periods, beginning with the estimates for the FY 1996 appropriation reveal a decline of 20.4 percent, 14.8 percent, and 40.8 percent, respectively. As mentioned this is primarily due to the number of increased applications being received for the NIEHS, while the amount available for competing grants has not kept up with inflation.

GRANTS TO WOMEN AND MINORITIES

Mr. Stokes: What is the success rate for research applications received from women researchers?

Dr. Olden: To comply with federal mandates, all questions related to race or gender are identified as optional on all NIH research grant applications. As a result, we are unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Last year, approximately 24 percent of our grant applicants choose not to complete the portion of the grant application referring to race and gender and have been coded in the "unknown" category. This varies from year to year. There is no way to predict the race or gender composition of those applicants. Thus, the available data may not provide a true representation of NIH's support of minority and women researchers. In FY 1994, the last year of actual data, the NIEHS success rate in general was 25.5 percent. The success rate for those who identified themselves as women researchers was 24.7 percent and for males it was 25.3 percent.

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Olden: For minorities who chose to answer the optional questions on the grant application related to race, the rate was 26.1 percent.

Mr. Stokes: What is the success rate for research applications received from African American researchers?

Dr. Olden: For African American Principal Investigators, no awards were identified. In making conclusions from the available data, it must be noted that 107 out of the 443 applications received, or 24 percent, and 27 of 113 awarded, or 24 percent, did not identify their ethnicity.

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Olden: The success rate for Historically Black Colleges and Universities for FY 1994 was 20 percent.

Mr. Stokes: What has been the trend in the average cost of the Institute's research project grants in general over that same time period?

Dr. Olden: Again, using FY 1994 data, the average cost of a competing grant is $209.2 thousand. The average cost of RPGs for FY 1995 is $217.8 thousand and for FY 1996 it is estimated that the average cost will be $227 thousand. From FY 1985 through FY 1994 ten year trend data for competing grants reveals that the average cost of a grant has risen from $157.0 to 209.2 thousand.

CONSTANT DOLLARS

Mr. Stokes: What does the trend look like in terms of constant dollars?

Dr. Olden: In constant dollars using the Biomedical Research and Development Price Index (BRDPI) with FY 1985 as the baseline, that same award with a 1985 cost of $157.0 thousand would have cost $236.1 thousand in 1994 dollars. Looking at it differently, we were only able to provide 87.2 percent of the funds necessary to keep pace with the BRDPI. By FY 1996, it would take $256.2 thousand to fund that same grant.

Mr. Stokes: For the same time period, in real and in constant dollars, what is the average costs of research project grants awarded to women?

Dr. Olden: As stated previously, questions related to gender are optional. The average cost for research project grants identified as being awarded to women in FY 1985 was $110.8 thousand and, using constant dollars, by FY 1994 the cost for that same award would be $166.6 thousand. The average amount actually awarded to women for FY 1994 was $228.0 thousand.

Mr. Stokes: For the same time period, in real and in constant dollars, what is the average costs of research project grants awarded to minority researchers?

Dr. Olden: As stated previously, questions related to race are optional on NIH grant applications. For those identified as minority researchers, the average cost in FY 1985 was $200.6 thousand and the average cost for FY 1994 was $154.1 thousand. Using the FY 1985 baseline the award issued in FY 1985 would cost $301.7 thousand in FY 1994.

Mr. Stokes: For the same time period, in real and in constant dollars, what is the average costs of research project grants awarded to African American researchers?

Dr. Olden: For African Americans, only one award was identified between FY 1985 and FY 1994, again, considering that questions related to the race of the applicant are optional. However, the Institute is making every effort to turn this trend around and is supporting African Americans in its minority supplements, minority faculty and educational outreach programs. It is believed this effort will yield fruits by increasing the pipeline of investigators who see opportunities in the Environmental Health Sciences fields and apply for funding opportunities through the NIEHS.

Mr. Stokes: For the same time period, in real and in constant dollars, what is the average costs of research project grants awarded to HBCUs?

Dr. Olden: For HBCUs, the statistics are similar, FY 1994 was the first year in which the NIEHS funded a grant at an HBCU institution. As stated previously the NIEHS is making every effort to change this situation. It is also important to state that based on the NIH Division of Research Grants data it is difficult to analyze trends for the NIEHS in isolation.

RACIAL IMBALANCE AT NIH

Mr. Stokes. According to a November 1993 article appearing in The Chronicle of Higher Education, white scholars received 90 percent of the research grants awarded competitively by the National Institutes of Health in 1991 according to a study by the agency. The study found that in the same fiscal year, Asians had received about 8 percent of such grants, Hispanic 1.5 percent, and African Americans 0.4 percent. What are the current statistics for your Institute?

Dr. Olden: As discussed earlier, questions related the the race of an applicant are optional. Based on competitive data for RPGs awarded by the NIEHS for FY 1994, the following percentages would apply: White scholars make up 74 out of 113, or 65.5 percent, Hispanic scholars account for 2 out of 113, or 1.8 percent, African American scholars account for 0 out of 113, or 0 percent, Asian scholars account for 10 out of 113, or 8.8 percent, and 27 out of 113, or 23.9 percent, are of unknown ethnicity. Data for the NIEHS portfolio as a whole, both competing and noncompeting combined, are currently unavailable. The NIEHS continues to work hard through meetings and advertising of programs to make the Institute more accessible to scholars who have been historically disadvantaged at competing for Institute funding opportunities.

MINORITY AND WOMEN'S HEALTH

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health indicated, in testimony before the committee this year, that the Department is enhancing its efforts to close the heath disparity gap. To what extent is minority health and women's health a priority for your Institute and why?

Dr. Olden: Minority health and women's health issues are top research priorities at NIEHS. The NIEHS, in cooperation with the NIH Office of Research on Minority Health, has a number of major efforts ongoing regarding minority health. A large clinical trial of a new treatment agent to lower blood lead levels in children is underway. We also have several basic research programs to understand how lead might be transferred from mothers to unborn children and how nutrition might be used as a way to avoid damage from maternally stored lead to the developing fetus.

We also support and conduct a variety of community outreach efforts through universities, medical schools, and our centers program. We expect that these communication activities will assist the public in taking whatever preventive actions are available to them to avoid exposures to environmental agents that might damage health. We are also training health care and research professionals specifically to deal with minority health issues. Regarding women's health, we are involved with the NCI in funding studies of the incidence of breast cancer in the northeastern U.S. and support several basic research programs on cancer and estrogens.

Mr. Stokes: What can you tell us this year that you could not tell us last year with regard to research progress in these two areas?

Dr. Olden: As you know, we arranged and co-sponsored a major conference on environmental justice this year. The purpose was to develop research strategies and agendas for health research programs in environmental equity. The agenda was designed to increase public participation in research planning and assure input from people historically under-represented and living in areas thought to be at high risk of exposure. The recommendations developed by the diverse groups and individuals at this conference are being used to design and "tune" new and existing programs of research and training.

In addition, I must mention the discovery of the BRCA1 breast cancer susceptibility gene several months ago by researchers at the NIEHS. This work, done cooperatively with university researchers, has opened the door to the development of a test for the gene which is implicated in early onset breast cancer in a large number of women.

CLINICAL TRIALS

Mr. Stokes: Clinical Trials appear to be the backbone for bridging basic research and advances in medical treatments. NIH Clinical Trials have yielded significant health benefits to the American people and have yielded comparable economic savings as well. What level of funding is included in your Institute's FY 1996 budget for clinical trials?

Dr. Olden: The NIEHS FY 1996 budget includes just under $3 million for clinical trials. Another $2.9 million is estimated to be provided from the Office of Research on Minority Health.

Mr. Stokes: How many trials would be funded and how many of these trials are new and how many are ongoing?

Dr. Olden: There is one clinical trial, the Treatment of Lead exposed Children (TLC) trial, mentioned previously, and it is on-going.

Mr. Stokes: Is there a specific system in place at your Institute for disseminating important information resulting from clinical trials?

Dr. Olden: Yes, NIEHS uses a system, MedLine, which is coordinated through the National Library of Medicine and is available to all Institute Directors. A good recent example of its use was Dr. L'Enfant's early release of trial data showing the benefit of hydroxyurea in the management and prevention of painful sickle cell crises.

Mr. Stokes: What progress is being made in increasing the numbers of women and minorities in clinical trials?

Dr. Olden: We have only one formal clinical trial, the Treatment of Lead-exposed Children Trial. It is primarily a study of minority children; mostly African-American, some Latino. We expect that it will enroll approximately equal numbers of boys and girls.

FTEs

Mr. Stokes: Is the Institute currently under a FTE freeze, and if so, how long has it been under this freeze and how is it impacting operations?

Dr. Olden: The Institute is not currently under a freeze. The NIH had been under a PHS-agency wide hiring freeze limiting hires to personnel within the Public Health Service since December 1993. The freeze was lifted in February 1995.

NIEHS is projecting FY 1995 FTE usage to be approximately 50 below ceiling. While we have been reassigning personnel from other areas to meet the highest priority needs, many programs are seriously understaffed producing inefficiencies and lost opportunities. Of particular concern has been our inability to fully implement the clinical program and to pursue leads in breast cancer and risk assessment. Certain support activities such as animal care and breeding and laboratory renovations here had to be contracted out at a cost greater than would have been required if done with federal employees.

However, like the rest of the Federal government, NIH is not exempt from the pressures of the Federal Workforce Restructuring Act and the requirements of the Administration's streamlining goals. Under the leadership of the Vice President, NIH, including this Institute, will continue to develop ideas and options for effectively managing our programs in this changing environment.

BREAST CANCER

Mr. Stokes: Nearly 200,000 new cases of breast cancer will be diagnosed this year, and an estimated 50,000 women will die from the disease. The committee heard testimony from the Secretary of HHS, the Assistant Secretary for Health, and the Director of the Center for Disease Control emphasizing that the overall death rate for breast cancer in American women declined about 5 percent between 1989 and 1992, the largest short-term decline in four decades. For white women in the 30 to 50 age group, death rates from breast cancer fell 8 to 9 percent over the same time period. However, for African American women, the rate of death due to cancer increased 2.6 percent. To what extent will this information be used to help focus the direction of research?

Dr. Olden: This disparity in death rates is unacceptable. It cannot be explained by any differences in genetic susceptibility that we currently know about. However, one of the reasons for our excitement about finding a gene that conveys susceptibility to breast cancer is that it allows us to learn more about susceptibility and to develop research strategies to find preventive and therapeutic interventions for this terrible disease. While this research goes forward at NIEHS, I will continue to work to assure that all of the information that is currently available on the importance of early diagnosis and treatment of breast cancer is communicated in a useful and meaningful way to African-Americans and other minority and disadvantaged Americans. I have given environmental health prevention communications my highest priority at NIEHS and have targeted our public communications efforts to disadvantaged minorities in communities affected by environmental injustice and to children in middle school and the environmental journalists.

Mr. Stokes: According to the Congressional Justification, the Institute's intramural researchers working with researchers in Utah, successfully isolated the breast cancer susceptibility gene, BRCA1. It further indicates that this gene accounts for 5 percent of breast cancers overall, and for 25 percent of early-onset of the disease in women under 30 years of age. What is the significance of this finding and what opportunities will this finding allow the Institute to further exploit?

Dr. Olden: The cloning of BRCA1 by NIEHS scientists represents a major breakthrough in breast cancer research. This discovery will provide new insights into the underlying mechanisms of breast, ovarian and possibly other cancers. The immediate opportunity from this discovery is the means to identify subpopulations of women at high risk for breast cancer. Understanding the function of BRCA1 may lead to new diagnostic tests and therapeutic regimens for breast and ovarian cancer. The mouse homolog of BRCA1 has already been cloned by NIEHS scientists and will allow development of new animal models for breast cancer that can be used to identify breast cancer carcinogens and to determine the effectiveness and side effects of new treatment therapies in animals before human studies.

Mr. Stokes: How much is included in the FY 1996 budget request to exploit these opportunities?

Dr. Olden: Of the $10.5 million in breast cancer research, more than $0.5 million is targeted for this specific area.

Mr. Stokes: To what extent is the Institute involved in implementing the Secretary's National Action on Breast Cancer, and how is the plan being used to help direct the focus of breast cancer research?

Dr. Olden: Breast cancer research has been given high priority at NIEHS. To a large degree, the emerging understanding of the relationship of environmental factors, particularly estrogen-like substances and breast cancer arose from research supported by NIEHS. This research and other studies at NIEHS helped set the stage for the HHS plan. We endorse the plan. Senior research scientists and managers from NIEHS participated in the development of the plan and are invested in assuring that it is implemented and we attain its goal.

Mr. Stokes: How much is included in the FY 1996 budget request for breast cancer, and how does this compare with the funding level for FY 1995 and FY 1994?

Dr. Olden: The FY 1996 budget request includes $10.5 million for breast cancer research. This compares with $7.0 million in FY 1995 and $3.4 million in FY 1994.

PROSTATE CANCER

Mr. Stokes: According to the Congressional Justification, prostate cancer is the most commonly diagnosed cancer among men in the United States. In testimony before the Committee last year the Director of the NCI emphasized that African American males have the highest rate of prostate cancer than any other segment of the world's population. To what extent has there been an increased prevalence of this disease in the last five to ten years?

Dr. Olden: Prostate cancer mortality in men over 65 years of age increased nearly 25 percent from 1973 to 1991.

Mr. Stokes: How much is included in the FY 1996 budget request for prostate cancer and how does this compare with the funding level for FY 1995 and FY 1994?

Dr. Olden: The FY 1996 budget request includes $551 thousand for NIEHS research on prostate cancer. This compares with $530 thousand for FY 1995 and FY 1994.

Mr. Stokes: Would you bring the Committee up-to-date on major activities that are underway with respect to unraveling the environmental factors associated with the development of prostate cancer?

Dr. Olden: Two features of the epidemiology of prostate cancer suggest the strong likelihood that environmental factors play an important role in the etiology of this disease. Mortality rates are elevated for African Americans, who have the highest rates in the world, and the mortality rates are substantially increased among African Americans in the southeastern United States. Although there are no well-documented environmental risk factors accounting for this distribution, several occupational groups, including farmers, welders, metal workers, textile dyers, and transport workers appear to be at increased risk. Exposure to agricultural chemicals, including pesticides and nitrate fertilizers may increase prostate cancer risk, especially among African Americans.

Several efforts are underway to address this important issue. First, the NIEHS, in collaboration with the NCI, has issued two Requests for Applications (RFAs) for research involving prostate cancer. Studies will include interdisciplinary studies that evaluate the effects of lifestyle factors, such as cigarettes and alcohol, occupations such as farming or industrial employment, environmental exposures such as radiation, PCBs and DDT, diet, xenoestrogens and the interrelationships of these factors with biological parameters and measures of genetic predisposition to cancer. The second RFA will support exploratory developmental grants to promote multidisciplinary research on prostate cancer.

There are several intramural studies underway that address the question of environmental risk factors for prostate cancer. For example, the Agricultural Health Study is a multi-year prospective study of cancer and chronic disease risk among 75,000 licensed pesticide applicators from North Carolina and Iowa. Quantifying the risk for prostate cancer associated with the use of agricultural chemicals is one of the major goals of this study. In addition, this study has recently added an initiative to enhance the enrollment of current and former African-American farmers. This will allow the investigators to address the potentially unique risk for prostate cancer in this population group.

FEDERAL ROLE IN INTRAMURAL RESEARCH

Mr. Stokes: In light of continuing fiscal constraints, in your professional judgement, why must the federal role in intramural research continue?

Dr. Olden: The mission of the NIEHS is to determine the health effects of environmental exposures, to communicate this information to an increasingly concerned public, and to train the nation's future cadre of environmental health scientists. These efforts require a multidisciplinary approach to environmental health science and NIEHS has developed intramural and extramural programs that capitalize upon the particular strengths of each.

The intramural program has developed a staff whose individual skills necessarily represent many scientific fields. The diverse composition of the intramural staff provides the nation with a unique resource in which the expertise from multiple specialties is pooled to address important environmental issues affecting the nation's health. This is true on a day-to-day basis where intramural scientists elucidate the basic mechanisms and environmental components of a number of important diseases including breast cancer, osteoporosis, respiratory disorders, neurotoxicity, and birth defects. This multidisciplinary team is also important during times of unanticipated environmental crises. Such events often require rapid, targeted research efforts to generate critical, new information; the NIEHS intramural staff has proven indispensable in this arena.

NIEHS has the principal responsibility within the Public Health Service for the National Toxicology Program (NTP). This interagency program is the nation's primary mechanism for characterizing the toxicity of environmental substances and for developing and validating alternative animal models for toxicologic effects. Research findings of this program are often the basis for regulatory decisions; the unquestioned high quality of NTP findings is significantly strengthening the nation's risk assessment process. Additionally intramural scientists are bridging the gap between new principles and techniques of molecular biology and classical toxicology. This "new toxicology" requires integrating the efforts of molecular biologists, classical toxicologists, epidemiologists, clinicians, and risk assessment experts. The multidisciplinary composition of the NIEHS intramural staff uniquely lends itself to these efforts.

GASOLINE ADDITIVES

Mr. Stokes: To what extent are you finding that the new gasoline additive requirements are creating a health problem?

Dr. Olden: Oxygenated fuels have been added to gasoline for the purpose of reducing emissions of hazardous air-pollutants such as carbon monoxide, especially during the winter months. A recent controversy has developed over the safety of one particular fuel oxygenate, methyl tert butyl ether (MTBE), which is added to gasoline at concentrations of up to 15 percent in some cities. A recent study has shown that MTBE causes tumors in laboratory animals exposed chronically to the chemical. However, high doses were required to produce those effects. In the human body, MTBE is changed to a chemical called tert butyl alcohol (TBA). A study has shown that TBA produces the same kinds of tumors in laboratory animals as does MTBE. Our evaluation of the available data on MTBE is that cancer risks from MTBE use are likely small for people who work in the petroleum industry or in gasoline stations or consumers who fill their own gas tanks. However, the NTP is continuing to look for ways to more precisely evaluate health risks of MTBE through laboratory experimentation.

ALZHEIMER'S DISEASE

Mr. Stokes: Is there cause to suspect and has research determined that there is a link between Alzheimer's Disease and environmental hazards?

Dr. Olden: At the present time there is cause to suspect, but no proven link between environmental toxics and Alzheimer's disease. Within the last few years a number of exciting results suggest that both genes and environment are involved in Alzheimer's diseases. As with cancer and heart disease, there seem to be several forms of Alzheimer's disease. Some of these disease forms appear to be influenced more heavily by genes or gene families. In all forms of Alzheimer's there seem to be persons who are susceptible vs. those who are resistant.

Leading environmental candidates for roles in Alzheimer's include metals like aluminum and iron, and pesticides. Alzheimer's plaques are rich in several metals, especially aluminum, but it is not yet clear, despite much research, whether metals cause or influence the formation of the plaques or whether the plaque is a convenient storehouse for the metals. Research has shown that essential metal deficiencies can influence the blood brain barrier leading to more penetration by toxic chemicals. Thus, iron deficiency can lead to more aluminum in the brain.

Recent studies suggest late-appearing neurological signs and deficits can occur in persons exposed to either toxic or moderately high doses of pesticides, sometimes years previously. Both Parkinsonism-like and Alzheimer's-like symptoms are seen in such persons.

WORKER TRAINING PROGRAMS

Mr. Stokes: By what authority does the NIEHS have responsibility for its worker training programs?

Dr. Olden: Section 126(g) of Superfund Amendments and Reauthorization Act of 1986 gives NIEHS authority to support worker training programs.

Mr. Stokes: Briefly describe the programs and their accomplishments.

Dr. Olden: Since the initiation of the Superfund Worker Training Grants Program in 1987, the NIEHS has developed a strong private and public partnership of organizations to deliver high-quality, peer-reviewed safety and health curriculum to target populations of hazardous waste workers and emergency responders. Employers have embraced these model training programs as a source of highly qualified workers for hazardous waste operations and emergency response.

During its first seven years, FY 1987-1994, the NIEHS Worker Education and Training Program has successfully supported eighteen primary awardee consortia, which include major universities, joint labor-management training funds, community colleges and unions who have trained over 400,000 workers in every state and presented over 20,000 classroom and hand-on training courses, which have accounted for over seven million contact hours of actual training. The program has innovated technically-proficient curriculum materials and quality-controlled course presentations and has established new national benchmarks for effective worker safety and health training. The program encourages participants to address the special training needs of under-served populations including issues such as: appropriate adult education; literacy; cultural and language differences; and other areas affecting hazardous waste workers and emergency responders. The program also has represented a major prevention education activity for NIEHS as technical scientific and basic research information is delivered to target populations with high risk toxic exposures.

During the past year, FY 1994, training delivery has been carried out in all regions of the country. The eighteen primary worker training awardees, in conjunction with over seventy collaborating institutions, have delivered 5,348 courses, reaching 87,205 workers.

Mr. Stokes: What is the FY 1996 funding level, and how does this compare with the FY 1995 funding level?

Dr. Olden: The NIEHS FY 1996 budget request to EPA for worker training to be conducted by NIEHS is $20 million for the Superfund worker training program and $3 million for the minority worker training program for a total of $23 million. The FY 1995 funding level is the same, $23 million.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

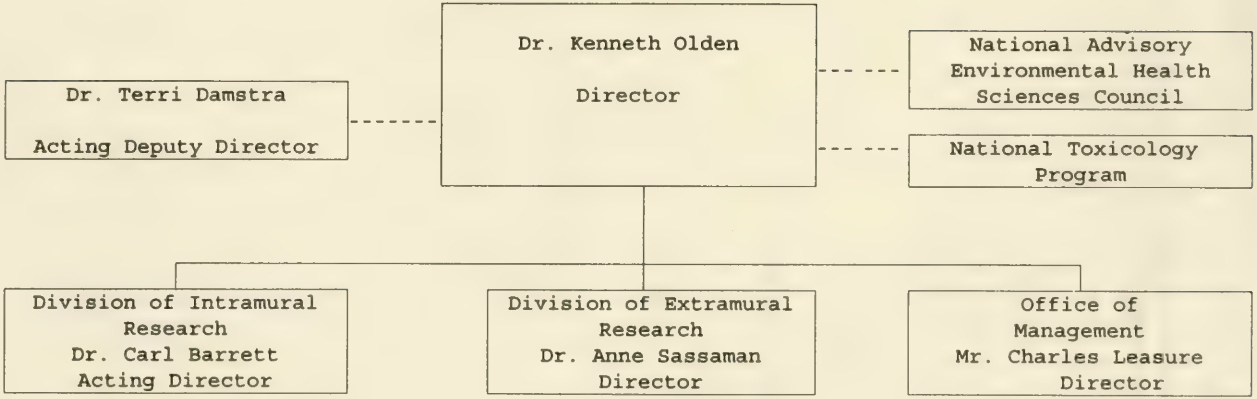
National Institute of Environmental Health Sciences

FY 1996 Budget	Page No.
Organization chart	88
Appropriation language	89
Amounts available for obligation	91
Budget mechanism table	92
Summary of changes	94
Budget authority by object	96
Administrative costs	98
Significant items in House and Senate Appropriations Committee Reports	99
Authorizing legislation	102
Appropriation history	103
Budget authority by activity	105
Justification:	
A. General statement	107
B. Extramural research	111
C. Intramural research	114
D. Research management and support	117
E. Detail of full-time equivalent employment (FTE)	119
F. Detail of end-of-year employment	120

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out Section 301 and 311 and title IV of the Public Health Service Act with respect to environmental health sciences, [$267,566,000] *$278,832,000*.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$264,249,000	$267,566,000	$278,832,000
Section 205 Procurement reduction....................		-366,000	
Section 207 Rent reduction......		-1,000	
Section 513 S&E reduction.......		-211,000	
Subtotal, Adjusted Appropriation..............	264,249,000	266,988,000	278,832,000
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities......	-5,608,000		
Subtotal, adjusted budget authority.........	258,641,000	266,988,000	278,832,000
Unobligated balance, lapsing......................	-132,000		
Total obligations..........	258,509,000	266,988,000	278,832,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1994--$70,849,000; 1995--$81,000,000; 1996--$81,000,000.

Also excludes funding for HIV activities: FY 1995--$5,745,000; FY 1996--$6,051,000, included in Office of AIDS Research, NIH.

Note: Excludes $16,000 in FY 1994 and $83,000 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	293	$67,048,000	308	$70,818,000	294	$67,627,000
Administrative supplementals	(17)	766,000	(10)	523,000	(10)	538,000
Competing:						
Renewal	39	8,377,000	31	6,712,000	43	9,691,000
New	73	15,245,000	58	12,647,000	75	17,050,000
Supplementals	1	17,000		--		--
Subtotal, competing	113	23,639,000	89	19,359,000	118	26,741,000
Subtotal	406	91,453,000	397	90,700,000	412	94,906,000
SBIR/STTR	15	2,131,000	20	2,571,000	20	2,707,000
Subtotal, RPG	421	93,584,000	417	93,271,000	432	97,613,000
Research Centers	20	20,016,000	20	21,072,000	20	21,072,000
Other Research:						
Research career programs	23	2,510,000	26	2,814,000	26	2,839,000
Minority biomed. res. support	--	441,000	--	462,000	--	462,000
Other research related	18	1,413,000	18	1,497,000	21	1,859,000
Subtotal, other research	41	4,364,000	44	4,773,000	47	5,160,000
Total, Research Grants	482	117,964,000	481	119,116,000	499	123,845,000

Training						
Individual awards:						
Noncompeting	32	815,000	22	546,000	22	546,000
Competing:						
New	14	328,000	24	615,000	24	615,000
Supplementals		14,000				
Subtotal, individ	46	1,157,000	46	1,161,000	46	1,161,000
Institutional awards:						
Noncompeting	374	8,030,000	313	7,969,000	313	7,969,000
Competing:						
Renewal	54	1,172,000	94	1,044,000	98	1,130,000
New	--	--	20	490,000	21	515,000
Supplementals	8	473,000	9	200,000	4	89,000
Subtotal, inst	436	9,675,000	436	9,703,000	436	9,703,000
Total, training	482	10,832,000	482	10,864,000	482	10,864,000
Research & Development Contracts	113	49,776,000	118	56,692,000	122	60,968,000
(SBIR/STTR)	(9)	(1,190,000)	(11)	(1,240,000)	(11)	(1,240,000)
	FTEs		FTEs		FTEs	
Intramural Research	599	70,374,000	602	70,540,000	597	73,061,000
Research Management and Support	103	9,695,000	105	9,776,000	104	10,094,000
Total, NIEHS	702	258,641,000	707	266,988,000	701	278,832,000
Clinical Trials		(3,309,000)		(3,207,000)		(2,991,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Summary of Changes

1995 Estimated budget authority	$266,988,000
1996 Estimated budget authority	278,832,000
Net change	+11,844,000

	1995 Current Estimate Base (FTEs)	1995 Current Estimate Base Budget Authority	Change from Base (FTEs)	Change from Base Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increases		$35,161,000		+$479,000
b. One more day of pay		35,161,000		+135,000
c. Annualization of January 1995 pay increases		35,161,000		+188,000
d. January 1996 pay increases		35,161,000		+600,000
e. Increase in unemployment compensation		207,000		+6,000
f. Increased cost of centrally furnished services		1,674,000		+282,000
g. Decreased cost of FTS		5,000		-1,000
h. Increased cost of Service and Supply Fund		1,644,000		+48,000
i. Increased cost of laboratory supplies, materials, and other expenses		32,061,000		+930,000
Total				+2,667,000
2. Research management and support:				
a. Within grade increases		6,025,000		+83,000
b. One more day of pay		6,025,000		+23,000
c. Annualization of January 1995 pay raise		6,025,000		+32,000
d. January 1996 pay raise		6,025,000		+103,000
e. Increased cost of centrally furnished services		962,000		+164,000
f. Increased cost of Service and Supply Fund		74,000		+2,000
g. Increased cost of laboratory supplies, materials, and other expenses		2,715,000		+78,000
h. Decreased cost of DHHS Working Capital Fund		315,000		-9,000
Total				+476,000
Subtotal				+3,143,000

Summary of Changes--continued

	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	308	71,341,000	-14	-3,176,000
b. Competing	89	19,359,000	+29	+7,382,000
c. SBIR/STTR	20	2,571,000	--	+136,000
Total	417	93,271,000	+15	+4,342,000
2. Other research	44	4,773,000	+3	+387,000
3. Research and development contracts	118	56,692,000	+4	+4,276,000
Subtotal, extramural				+9,005,000
	(FTEs)		(FTEs)	
4. Intramural research	602	70,540,000	-5	-146,000
5. Research management and support	105	9,776,000	-1	-158,000
Subtotal, program				-304,000
Total changes				+11,844,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment..............	707	701	-6
Full-time equivalent of overtime and holiday hours.........	4	4	---
Average ES salary....................	$111,737	$114,195	+2,458
Average GM/GS grade..................	10.44	10.44	---
Average GM/GS salary	46,945	48,823	+1,878
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)..................	73,444	75,060	+1,616
Average salary of ungraded positions.	31,315	32,004	+689
Personnel compensation:			
Full-time permanent	$26,011,000	$26,710,000	+$699,000
Other than full-time permanent.....	5,215,000	5,677,000	+462,000
Other personnel compensation.......	611,000	621,000	+10,000
Special personnel service payments.	2,847,000	2,886,000	+39,000
Total personnel compensation....	34,684,000	35,894,000	+1,210,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Personnel benefits	6,327,000	6,462,000	+135,000
Benefits for former personnel.....	175,000	25,000	-150,000
Travel and transportation of persons....................	1,146,000	1,269,000	+123,000
Transportation of things..........	149,000	185,000	+36,000
Rental payments to GSA...........	513,000	528,000	+15,000
Rental payments to Others.........	647,000	666,000	+19,000
Communications, Utilities, and Miscellaneous Charges...........	4,738,000	4,998,000	+260,000
Printing and reproduction.........	681,000	821,000	+140,000
Other services:			
Consulting services.............	105,000	108,000	+3,000
Other...........................	13,607,000	14,143,000	+536,000
Purchases from Govt. Accts......	11,119,000	11,378,000	+259,000
R&D contracts...................	50,599,000	54,775,000	+4,176,000
Supplies and materials...........	7,856,000	8,079,000	+223,000
Equipment........................	4,657,000	4,792,000	+135,000
Grants, subsidies & contributions.	129,980,000	134,709,000	+4,729,000
Interest and dividends...........	5,000	--	-5,000
Total budget authority by object................	266,988,000	278,832,000	+11,844,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Administrative Costs

	1995 Current Estimate	1996 Estimate	Decrease or Increase
Personnel compensation:			
Full-time Permanent (11.1)	$26,011,000	$26,710,000	+$699,000
Other than Full-time Permanent (11.3)	5,215,000	5,677,000	+462,000
Other Personnel Compensation (11.5)	611,000	621,000	+10,000
Special Personnel Compensation (11.8)	2,847,000	2,886,000	+39,000
Total Personnel Compensation	34,684,000	35,894,000	+1,210,000
Personnel benefits (12.1)	6,327,000	6,462,000	+135,000
Benefits for former personnel (13.0)	175,000	25,000	-150,000
Travel (21.0)	1,146,000	1,269,000	+123,000
Transportation of things (22.0)	149,000	185,000	+36,000
Rental payments to Others (23.2)	647,000	666,000	+19,000
Communications, Utilities, and Miscellaneous Charges (23.3)	4,738,000	4,998,000	+260,000
Printing and reproduction (24.0)	681,000	821,000	+140,000
Consulting services (25.1)	105,000	108,000	+3,000
Other Services (25.2)	13,607,000	14,143,000	+536,000
Purchases from Govt. Accts (25.3)	3,762,000	3,921,000	+159,000
Supplies and materials (26.0)	7,856,000	8,079,000	+223,000
Total	73,877,000	76,571,000	+2,694,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Significant Items in House and Senate Appropriations Committee Reports

1995 House Report	Action Taken or to be Taken
National Toxicology Program	
1. "The Committee is concerned by the reduced number of carcinogenicity test starts for long term chronic diseases in the National Toxicology Program (NTP) in recent years. The Committee is dismayed to learn that only four chronic carcinogenicity tests have been started in 1994, fewer than the Committee's recommended number of at least 15 starts. Therefore, the Committee urges that, substantially more than 15 new chemicals or substances, or combination of substances, studies be started in 1995 for identifying potential carcinogenicity using the current standard NTP experimental two-year design protocol." (Report No. 103-553, page 57)	1. The NTP is working to increase the number of chemicals under test, as well as the quality of tests and the relevance of rodent bioassays to risk assessment. The start of new tests has been impacted by the chemical nomination process and the time necessary to award contracts for study starts. During FY 1995 we will award contracts for 32 two-year rodent bioassays. Due to the prechronic studies and other data required preliminary to actually dosing animals, 4 chemicals will start on the two-year bioassay phase in FY 1995. Bioassays of the other 28 chemicals will start in FY 1996 and FY 1997. An additional 21 chemicals have been approved by the NTP Chemical Evaluation Committee and the NTP Executive Committee for future carcinogenicity studies.

Significant Items, Continued

Training	Action Taken or to be Taken
2. "To ensure that an adequate workforce of scientists exists in the fields of toxicology, epidemiology and certain engineering disciplines essential to solving environmental problems threatening public health, the Committee strongly encourages NIEHS to expand its academic awards to centers of excellence in environmental and occupational health." (Report No. 103-553, page 57)	2. The NIEHS continues its strong commitment to ensuring that an adequate workforce of scientists exists for addressing environmental issues. As such, the Institute has utilized its centers as one means of expanding the workforce in critical environmentally related fields such as toxicology, epidemiology, etc. This has been accomplished by requiring outreach and education activities at centers and through the award of Environmental/ Occupational Medicine Academic Awards. In the five years since its inception, fourteen of these academic awards have been made, half to institutions where environmental centers presently exist. The NIEHS plans to continue its commitment to the Environmental/Occupational Medicine Academic Awards program as a means of building the workforce for addressing critical environmental problems into the next century. Centers will continue to play a vital role in this process.

Significant Items, Continued

1995 Senate Report

Parkinson's Disease	Action Taken or to be Taken
1. "The Committee encourages further efforts to stimulate research in this area within the funds provided, including the convening of a scientific workshop. The Committee also urges the Institute to work with NINDS to incorporate this area of research as part of the agenda for the consensus conference on Parkinson's disease and related neurodegenerative disorders which the Committee directs the NINDS to undertake in fiscal year 1995." (Report No. 103-553, page 91)	1. The NIEHS research effort on Parkinson's Disease focuses on understanding the role of environmental exposure in the development of this debilitating disease. NIEHS is supporting and conducting epidemiologic research on exposure to metals such as manganese, zinc, and mercury. Previous research established an association between high mercury exposure and the development of Parkinson's disease later in life. Additional NIEHS research is targeted toward understanding the basic cellular mechanisms in brain cells, and how these mechanisms are damaged after exposure to environmental agents. Elucidating these events will aid in establishing links between environmental exposures and Parkinson's disease and aid public health officials in developing strategies to prevent exposure and thus prevent disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation...........	Section 301	42§241	Indefinite	$256,124,000	Indefinite	$267,968,000
National Institute of Environmental Health Sciences................	Section 463	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards..................	Section 487(d)	42§288	Such sums as necessary	10,864,000	Such sums as necessary	10,864,000
Total, Budget Authority.............				$266,988,000		$278,832,000

NATIONAL INSTITUTES OF HEALTH

National Institutes of Environmental Health Sciences

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	$187,995,000	$209,872,000	$208,067,000	$209,294,000
1988	198,431,000	225,724,000 3/	220,709,000	215,666,000
1989	218,471,000 4/	216,985,000 5/	223,168,000	223,454,000 6/
1990	226,471,000 7/	232,479,000	234,048,000	232,476,000 8/
1990 Sequester				-3,242,000
1991	235,792,000	244,832,000 9/	242,765,000	241,028,000 10/
1992	254,484,000	254,912,000	250,873,000	251,575,000 11/
1993	261,513,000	252,564,000	255,115,000	251,187,000 12/
1994	261,306,000	264,249,000	264,249,000	264,249,000
1995 13/	267,955,000	266,400,000	267,955,000	266,988,000 14/
1996 13/	278,832,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance spread the funding among the Institutes, including $216,000 for NIEHS.

3/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

4/ The 1989 request excludes funding for AIDS research and education ($4,234,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $9,183,000 in NRSA training programs not considered.

6/ Excludes enacted administrative reduction of $2,714,000.

7/ The 1990 request excludes funds for the National HIV program ($4,377,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

8/ Excludes enacted administrative reduction of $788,000.

9/ Excludes $10,586,000 in NRSA training programs not considered.

10/ Excludes enacted administrative reduction of $8,064,000.

11/ Excludes enacted administrative reductions of $4,871,000 and $456,000. Includes $3,000,000 real transfer from the National Cancer Institute.

12/ Excludes enacted administrative reduction of $3,928,000.

13/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

14/ Excludes enacted administrative reductions of $366,000, $1,000, and $211,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Biological response to environ agents..		$73,215		$75,154		$82,336		$82,359		$86,242		+$3,883
Applied toxicological res. and testing		55,045		53,336		54,861		62,235		66,996		+4,761
Biometry and risk estimation.........		11,584		8,943		10,527		10,142		10,503		+361
Resource and manpower development..		27,840		27,986		30,847		31,936		31,936		--
Subtotal..		167,684		165,419		178,571		186,672		195,677		+9,005
Intramural research..	673	70,370	653	72,226	599	70,299	602	70,540	597	73,061	-5	+2,521
Research management and support.......	95	9,214	97	9,138	103	9,639	105	9,776	104	10,094	-1	+318
Total obligations....	768	247,268	750	246,783	702	258,509	707	266,988	701	278,832	-6	+11,844
Unobligated balance lapsing...........	--	82	--	132	--	132	--	--	--	--	--	--
Total Budget Authority.........	768	247,350	750	246,915	702	258,641	707	266,988	701	278,832	-6	+11,844

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Environmental Health Sciences

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
702	$258,641,000	707	$266,988,000	701	$278,832,000	-6	+11,844,000

General Statement

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility, and time and or age. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.

The NIEHS mission is extremely important. Diseases and dysfunctions with an environmental component include cancer, birth defects, infertility, neurological impairments, immune disorders, and lung dysfunction. Because environmental exposures can be controlled or avoided, they represent one of the most promising means of improving our Nation's health. NIEHS-supported research will play increasingly important roles in helping policy makers design primary prevention schemes that restrain costs both of health care and of regulatory compliance.

This past year has yielded significant returns on NIEHS' long-term investments in basic environmental health research, prevention, and communication. Current research activities include:

- *Nobel Prize for G protein Research:* NIEHS Scientist Emeritus, Dr. Martin Rodbell, was co-recipient of the 1994 Nobel Prize in Medicine/Physiology. Dr. Rodbell studies the mechanisms by which cells communicate with each other and his work on G proteins was the subject of the Nobel Prize. Cell communication systems are a target for many environmental agents and it is thought that damaged cell communication systems may underlie the development of many diseases.

- *Breast Cancer Susceptibility Gene:* The breast cancer susceptibility gene, BRCA1, was isolated through the collaborative efforts of NIEHS intramural scientists and colleagues in Utah. An inherited susceptibility to breast cancer due to mutations in BRCA1 is thought to account for 5% of breast cancer cases overall and 25% of early-onset (women under age 30) breast cancer cases. Isolating the BRCA1 gene brings us closer to understanding the origins of breast cancer. Of significance to the NIEHS, identification of breast cancer susceptibility genes will enable us in the future to define environmental components of breast cancer development in terms of individual genetic susceptibilities.

- *Public Information:* A toll-free Clearinghouse on Environmental Health Effects was established to give the American public better access to federally generated information on environmental health issues. The Clearinghouse handles a vast array of topics, including information on health effects from occupational exposures, hazardous waste sites, chemical spills and releases, and environmental justice issues. Additionally the Clearinghouse can refer callers to other relevant organizations in both the public and private sectors, can conduct online computer searches, and can mail NIEHS publications to callers.

- *Advancing Risk Assessment Methodology:* The NIEHS manages the large testing program of the National Toxicology Program (NTP). The toxicologic information generated by NTP chemical studies in rodents, fish, insects, and cell systems is the foundation for much of the risk assessment done by regulatory agencies. New developments in molecular biology, if incorporated into toxicity assays, offer exciting opportunities for advancing the specificity and relevance of risk assessment schemes. Incorporating this mechanistically-based toxicology into risk assessments, however, requires the cooperation and agreement of many parties. These parties include federal law makers and their staff, industry, regulatory agencies, toxicologists, and advocacy groups. The NIEHS/NTP hosted special workshop to be held January 11 - 13, 1995, will begin this vital dialogue. It will be the first time that **all** invested parties meet together to discuss the implications to research, regulation, and legislation of newly evolving techniques for using mechanism-based toxicology in cancer risk assessment. Recommendations from this workshop will provide a framework for developing risk assessment schemes and prevention programs that will enhance our ability to protect the public's health from environmentally caused diseases while maintaining economic vitality.

The President's appropriation request of $278,832,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NIEHS during the past five years has been as follows:

	Amount	FTE
FY 1991	$236,119,000	746
FY 1992	247,350,000	768
FY 1993	246,915,000	750
FY 1994	258,641,000	702
FY 1995	266,988,000	707

Purpose and Method of Operation

The purpose of NIEHS' research is to provide a good understanding of how environmental factors, interacting with individual genetic susceptibilities over the course of a lifetime, can lead to diseases and disabilities. NIEHS and public policy agencies use this information to define public risks, to devise prevention and intervention strategies in the treatment of environmentally induced diseases, and to communicate the risks and risk-reduction techniques to the public.

The investigator-initiated research project grant program is the Institute's primary mechanism for supporting studies conducted by university scientists. These studies involve programs related to biological response to environmental agents, applied toxicological research and testing, and biometry and risk estimation. The scientists use all available tools of biomedical research, including basic biomedical studies, epidemiology, and toxicology. For the most part, this mechanism supports either a discrete, specified project by the named investigator or a broadly based, multidisciplinary program that includes several projects that have a specific major objective or basic theme.

Through grants to research centers it is possible to assemble a critical mass of scientific talent and apply it to the complex scientific questions which typify all environmental health problems. Supplemental funds are available to the centers for data collection and evaluation in the event of major accidents or disasters. In addition, the centers can support small pilot projects that enable a researcher to determine if a comprehensive research grant application is feasible.

Through the research career program, the Institute supports career development of researchers by issuing research career development awards, academic/teacher awards, clinical investigator awards, and physician-scientist awards. This mechanism also supports the Environmental/Occupational Medicine Academic awards. Other research grant awards support major conferences, small instrumentation, and scientific review and evaluation activities.

The National Research Service Award program supports research training of scientists for careers in basic and applied research into the human health implications of environmental exposures. The training is concentrated in the areas of toxicology, pathology, reproductive biology, mutagenesis, epidemiology and biostatistics, and molecular biology. Fellowship awards are made to individuals and training grants are made to institutions. The goal is to supply the critical scientific expertise necessary to solve environmental health problems encountered by individuals, patients, and the community in which they reside. It is also the goal of this program to reach out to under-utilized populations, such as minorities and women, and encourage their participation as members of the environmental health sciences workforce.

The research and development contract mechanism is used to support specific research studies characterizing chemical toxicity and improving the testing methods used to determine toxicity and to support studies in basic and applied statistics, biomathematics, epidemiology, molecular modeling, and risk assessment.

The intramural research activity is made up of three major scientific programs plus associated technical and administrative support. The Environmental Toxicology Program is the lead program for NTP responsibilities; it plans and directs toxicology and carcinogenesis studies that characterize the toxicity of environmental agents. The Environmental Carcinogenesis Program studies the pathological, cellular, and molecular basis of cancer in humans and experimental animals and the effects of environmental agents on these processes. The Environmental Biometry and Epidemiology Program conducts basic research in statistics, epidemiology, and biomathematics related to the assessment of risk from exposure to environmental agents.

The research management and support activity provides salary and other support for the Office of the Institute Director, the Division of Extramural Research and Training, and portions of the Office of Management.

Overall Budget Policy

The FY 1996 budget request for NIEHS is $278,832,000, an increase of $11,844,000 over the FY 1995 estimate. Seventy percent of the budget request would support research grants, training, and contract activities, and 30 percent of the request would support intramural research and research management activities.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

The FY 1996 budget request includes $97,613,000 for 432 research project grants, compared to $93,271,000 for 417 grants in FY 1995. Within this total 118 competing grants will be funded at an average cost of $226,600, an increase of 29 awards over FY 1995 and an increase of 4.2% in average cost. The anticipated success rate in the budget request is 21.9 percent. The FY 1996 budget request would support 294 noncompeting research project grants at an average cost of $230,000, a decrease of 14 awards from FY 1995.

Fifteen environmental health sciences centers and five marine and freshwater biomedical sciences centers would receive $21,072,000 in support from this request, the same as in FY 1995. Other research grants would receive $5,160,000, an increase of $387,000 and three awards over FY 1995.

The FY 1996 request would support 482 research trainees at an estimated cost of $10,864,000, the same as in FY 1995.

Contracts to support research and development in toxicity testing and test development, in risk estimation methods, and for other scientific problems in environmental health are projected at $60,968,000. Approximately 122 contracts would be supported, an increase of $4,276,000 and four awards over FY 1995.

The budget request for intramural research is $73,061,000 and 597 FTEs, an increase of $2,521,000 and a decrease of five FTEs from FY 1995. The request for research management and support is $10,094,000 and 104 FTEs, an increase of $318,000 and a decrease of one FTE.

National Institute of Environmental Health Sciences

Extramural Research

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$178,572,000	$186,672,000	$195,677,000	+$9,005,000

Institute-supported grantees and contractors contribute to the success of its mission through free-ranging and directed research in biological response to environmental agents, applied toxicological research and testing, and biometry and risk assessment. Also, NIEHS supports the development of key national resources in environmental public health and the training of environmental health scientists through three major grant programs: environmental health sciences core centers, marine and freshwater biomedical sciences centers, and National Research Service Award (NRSA) grants.

Funding for this activity during the past five years has been as follows:

	Amount
FY 1991	$160,588,000
FY 1992	167,705,000
FY 1993	165,419,000
FY 1994	178,572,000
FY 1995	186,672,000

Rationale for the Budget Request

The FY 1996 budget request for Extramural Research is $195,677,000, an increase of $9,005,000 over the FY 1995 estimate of $186,672,000. These funds will provide support for the following activities: biological response to environmental agents, $86,242,000, an increase of $3,883,000 or 4.7 percent over the FY 1995 estimate of $82,359,000; applied toxicological research and testing, $66,996,000, an increase of $4,761,000 or 7.7 percent over the FY 1995 estimate of $62,235,000; biometry and risk estimation, $10,503,000, an increase of $361,000 or 3.6 percent over the FY 1995 estimate of $10,142,000; and resource and manpower development, $31,936,000, the same as the FY 1995 estimate.

The NIEHS extramural research community collectively represents the greatest concentration of talent focused on environmental health concerns in this country. Their research necessarily spans the entire spectrum of human health endpoints. Some important ongoing efforts include:

Breast Cancer

One out of every nine women in the United States develops breast cancer. Known risk factors include family history of breast cancer, reproductive history, and obesity. However, 70% of women who develop breast cancer have none of the known risk factors. Clearly an environmental component accounts for many cases of breast cancer development. Identification of environmental components of breast cancer is complicated by the fact that individual susceptibility and the age of exposure seem to be major determinants in how environmental exposures exacerbate a woman's risk of developing breast cancer. The NIEHS extramural community is focusing on a number of promising research projects aimed at better understanding the development of breast cancer. Because breast cancer seems to be estrogen related, many of these projects examine the association between environmental estrogenic compounds, such as pesticides and dioxin, and breast cancer development. Other projects are aimed at identifying those environmental agents that have estrogenic and anti-estrogenic effects. Other studies are assessing how the timing of critical exposures lead to increased risk of breast cancer.

Susceptibility and Risk Assessment

Biomarkers are important biological "road signs" that a living organism has come into contact with, or been affected by, an environmental agent. The NIEHS supports an active research portfolio in biomarker development. The end product of these efforts will be incorporation of biomarkers into human epidemiologic studies that can more precisely define the health effects of specific environmental exposures. Current efforts include: development of immunohistochemical techniques to detect the presence of the grain mold toxin, aflatoxin, in DNA from liver tumor tissue; analysis of environmental chemical metabolites that bind to hemoglobin and give a quantifiable indication of an individual's exposure to the bladder carcinogen, 4-aminobiphenyl; use of accumulation of specific porphyrins in human urine as a measure of mercury exposure; and the use of sperm structure and function as an indication of environmental exposures that could lead to reproductive dysfunction. Biomarkers have also been developed which detect activation of genes in response to exposure to a number of chemicals, including dioxin and environmental estrogens.

"Jackpot" Region for Environmentally Induced Mutations

Many environmental carcinogens act by attaching to critical genetic material and mutating it to another form. This new form can result in uncontrolled cell growth, or cancer. Understanding regions of DNA that are particularly susceptible to environmentally caused mutations will help us identify the mechanism of action of environmental carcinogens. NIEHS-supported scientists have developed a new technique, the mismatch amplification mutation assay (MAMA) in rat mammary tissue that identifies areas on the gene that are particularly susceptible to mutations that result in cancers. These areas are called "jackpot" regions and appear to require more than one mutational insult to give rise to cancer.

Adaptation to Environmental Insult - Cadmium

High levels of cadmium are toxic and they cause pulmonary edema, hemorrhage in the lung and difficulty in breathing. People are exposed to cadmium by breathing contaminated air from a variety of sources, including spray painting, industrial electroplating, cigarette smoke, gases from fossil fuel and solid waste combustion. A recent NIEHS-supported study showed that repeated exposures to aerosols of cadmium does not produce a long-lasting injury to the lung; rather, the lungs appear to adapt and develop a tolerance to it. Work will continue to determine the biochemical and molecular mechanisms responsible for this apparent tolerance. One study found that a protein called metallothionein accumulates in lungs exposed to cadmium, but not in lungs exposed to air alone. This study suggests that metallothionein may protect the lung against the toxic effects of cadmium and that this protein could be used to prevent lung injury.

Transgenic Animal Models

One of the greatest challenges of environmental health research is understanding how environmental agents interact with genes in ways that contribute to disease and dysfunction. A powerful new technology - the development of transgenic animal models - offers exciting opportunities for exploring the interaction of environmental exposures with critical genes. The NIEHS is supporting a number of researchers who create laboratory animals containing genetic alterations that will allow us to study the importance of environmental exposures and the timing of these exposures in development of numerous disease states.

National Institute of Environmental Health Sciences

Intramural Research

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
599	$70,374,000	602	$70,540,000	597	$73,061,000	-5	+$2,521,000

Institute scientists specialize in epidemiology, basic research, and toxicology. Through their participation in the National Toxicology Program, NIEHS intramural scientists are uniquely positioned to conduct research that is responsive to public, regulatory, and industry needs and to translate basic science into "real world" applications.

Funding for this activity during the past five years has been as follows:

	Amount	FTE
FY 1991	$67,335,000	656
FY 1992	70,424,000	673
FY 1993	72,333,000	653
FY 1994	70,374,000	599
FY 1995	70,540,000	602

Rationale for the Budget Request

The FY 1996 budget request for Intramural Research is $73,061,000, an increase of $2,521,000 over the FY 1995 estimate of $70,540,000. The following are examples of efforts supported by this budget activity.

NIEHS intramural research focuses on two major research areas. The first area involves understanding the basic mechanisms of environmental disorders. Important mechanisms include receptor- and hormone-mediated pathobiology, events controlling cell proliferation and cell death, genetic control of susceptibility to diseases, and the biological mechanisms regulating cellular communication, differentiation, and development. The other research area involves indentifying and characterizing environmental causes of diseases. Intramural scientists use information generated from these two research areas to develop workable prevention and treatment strategies to reduce the incidence of environmentally associated diseases. Some significant outgrowths of this research are:

Breast Cancer Susceptibility Gene

NIEHS scientists, working with researchers in Utah, have successfully isolated the breast cancer susceptibility gene, BRCA1. BRCA1 is thought to account for 5% of breast cancer cases overall and for 25% of early-onset, women under age 30, breast cancer cases. The discovery of the exact location of this gene brings us significantly closer to understanding the origins of breast cancer and enhances our ability to identify women at higher risk of developing this devastating disease. Of special significance to the NIEHS is the isolation of this gene. This will enable us to better study the ability of different environmental agents to mutate a gene that controls cellular events critical to the development of many cases of breast cancer.

Estrogen Receptor "Knockout Mouse"

The female hormone, estrogen, directs and controls cell growth and differentiation by binding to important estrogen receptor proteins located in tissues throughout the body. Many environmental compounds bind to these same receptor proteins, thus potentially acting as "environmental estrogens." Examples of environmental estrogens included many of the chlorinated pesticides such as DDT and kepone, polychlorinated biphenyls, and natural plant products in our diet. These environmental compounds, although weakly estrogenic, may play a role in a wide range of diseases. In women they may be implicated in development of endometriosis, uterine fibroids, and cancers of the breast, uterus, and ovaries. In men, these compounds might explain the decline in sperm quality seen over the past century. NIEHS intramural scientists, collaborating with researchers at the University of North Carolina at Chapel Hill, have developed a transgenic mouse that can aid in defining the role of environmental estrogens in human diseases and dysfunctions. In this mouse an important estrogen receptor has been "knocked out," thereby allowing investigators to evaluate the mechanism of action of hormonally active xenobiotics. This mouse model will be used to study actions of estrogenic chemicals in a variety of organ systems, including the reproductive tract, skeleton, cardiovascular system, and brain.

Alternative Animal Models

Several genetically altered, transgenic mice are available commercially. NIEHS intramural scientists are evaluating the usefulness of these new animal models in toxicologic testing. At present these studies indicate that these models could, in some cases, be valid substitutes for traditional two-year studies in rats and mice. The transgenic models yield results in six months, rather than two years, are able to produce results using fewer animals than traditional toxicologic studies, and offer a better dosimetry than currently available. The NIEHS will be working with regulatory agencies and law makers to determine ways in which these transgenic animals can be used in risk assessment schemes.

Environmental Causes of Birth Defects

Birth defects are the leading cause of infant mortality and childhood disability in this country. Every year 150,000 babies are born with serious birth defects of which 60% have no identifiable cause. In many of these cases an environmental component is suspected, but has been difficult to prove. A recent study by NIEHS epidemiologists, using data from a population-based registry of birth defects in Norway, provides further support for an environmental component in the development of birth defects. The records of over 370,000 mothers were examined. It was found that women who gave birth to a child with a birth defect were at higher risk of producing a second child with a birth defect. This risk, however, was reduced by half if the mother moved to another town. This finding indicates that environmental exposures could play a significant role in development of birth defects.

NTP Database to Identify Anti-Carcinogens

More than 400 cancer studies in rats and mice have been done by the National Toxicology Program (NTP) and its predecessor, the NCI Cancer Bioassay Program. This database offers a rich resource of information on cancer causing chemicals. Two intramural scientists recently demonstrated a more novel use of this database--the identification of anticancer activity of the chemicals studied. A number of chemicals were identified that actually served to reduce the number of spontaneous tumors. Most of the chemicals exhibiting such anticancer activity, however, did so in the presence of reduced body weight gain. Thus this activity might be accounted for by the lack of caloric intake, a known technique for reducing cancer incidence. In several instances, though, test animals gained weight at the same rate as control animals, but had much lower incidence of spontaneous tumors. These latter chemicals could serve as a basis for identifying preventive chemotherapies.

National Institute of Environmental Health Sciences

Research Management and Support

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
103	$9,695,000	105	$9,776,000	104	$10,094,000	-1	+$318,000

This budget activity supports the staff and related expenses involved in the overall management of the Institute. Included are activities such as the Director's immediate office, individuals responsible for communications, the planning and evaluation function and the review and management of the Institute's grant and contract programs.

Funding for this activity during the past five years has been as follows:

	Amount	FTE
FY 1991	$8,196,000	91
FY 1992	9,221,000	95
FY 1993	9,163,000	97
FY 1994	9,695,000	103
FY 1995	9,776,000	105

Rationale for the Budget Request

The FY 1996 budget request for Research Management and Support is $10,094,000, an increase of $318,000 over the FY 1995 estimate of $9,776,000. Research management and support funds several organizational units charged with carrying out Institute-wide responsibilities. These units are the Office of the Director, the Division of Extramural Research and Training, some portions of the Office of Management, and the Office of Communications.

Establishment of New Public Information Program

A toll-free Clearinghouse on Environmental Health Effects was recently established to allow the American public better access to federally generated information on environmental health issues. The Clearinghouse handles a vast array of topics, including information on health effects from occupational exposures, hazardous waste sites, chemical spills and releases, and environmental justice issues. Additionally the Clearinghouse refers callers to other relevant organizations in both the public and private sectors, conducts online computer searches, and can mail NIEHS publications to callers.

Environmental Justice

The Institute will continue its activities in this important area during this fiscal year. The national meeting sponsored by NIEHS in January of 1994 produced a series of recommendations that forms the basis for further actions in the future. While specific projects in this program will be funded from all of the budget mechanisms, the overall direction and management will be located in the Office of the Director. The Office of Communications and the Office of Institutional Development will share much of the responsibility, particularly for the outreach and community involvement portions. The January meeting helped to establish a dialogue and credibility with a number of groups and these interactions will be strengthened during the year.

Streamlining

The reorganization of the Institute that was completed last year has produced numerous savings in personnel and dollars as reflected in the FY 1996 budget. These activities will continue and further adjustments in command and control positions and in the Office of the Director will be made. In making these reductions, the Institute will rely heavily on input from a series of committees made up of employees from all divisions and grade levels. The recommendations from these groups will help management to focus available resources in such a way as to produce the greatest efficiencies and the best science. A new program of cross-training for administrative personnel will be undertaken so that the highest priority functions can be continued utilizing savings from less critical areas.

Building Addition

The new laboratory module will become operational in late FY 1996 and will allow for the transfer of the remaining scientists from the leased facilities where they have been since the Institute was founded in the late 1960s. This move will reduce rental and support costs significantly and most importantly will bring together all of the intramural scientists, the library, animal facilities and other research support under one roof. Additional funding will allow for the increased capacity of the utility systems necessary to ensure the safe and uninterrupted operation of research projects. With these utility requirements completed, this phase of the building program will be finished.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Appropriation	1996 Estimate
Office of the Director......................	88	72	69
Division of Intramural Research.............	434	441	441
Division of Extramural Research and Training.................................	41	50	50
Office of Management.......................	139	144	141
Total, NIEHS............................	702	707	701

Average GS/GM Grade

1991....................................	10.01
1992....................................	10.13
1993....................................	10.30
1994....................................	10.44
1995....................................	10.44
1996....................................	10.44

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute of Environmental Health Sciences

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-5	1	1	1
ES-4	9	10	10
ES-3	1	--	--
Subtotal	11	11	11
Total - ES Salary	$1,215,745	$1,229,111	$1,256,152
GS/GM-15	36	37	37
GS/GM-14	51	46	44
GS/GM-13	53	58	58
GS-12	62	61	60
GS-11	94	97	96
GS-10	3	2	2
GS-9	63	62	62
GS-8	23	23	23
GS-7	72	72	72
GS-6	30	30	30
GS-5	22	22	21
GS-4	32	33	33
GS-3	26	26	26
GS-2	2	2	2
Subtotal	569	571	566
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	7	6	6
Senior Grade	8	9	9
Subtotal	15	15	15
Ungraded	116	119	118
Total permanent positions	541	546	546
Total positions, end of year	711	716	710
Total full-time equivalent (FTE) employment,end of year	702	707	701
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$110,522	$111,737	$114,195
Average GS/GM grade	10.44	10.44	10.44
Average GS/GM salary	$44,949	$46,945	$48,823

TUESDAY, MARCH 15, 1995.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE

WITNESSES

CLAUDE LENFANT, DIRECTOR

DR. BARBARA PACKARD, ASSOCIATE DIRECTOR FOR SCIENTIFIC PROGRAM OPERATIONS

JAMES WEHLING, FINANCIAL MANAGEMENT OFFICER

MARYANN GUERRA, EXECUTIVE OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. The committee will come to order.

We continue our hearings on the National Institutes of Health with the National Heart, Lung and Blood Institute. And we're delighted to welcome the Director, Dr. Claude Lenfant. Why don't you proceed any way you wish. We'd appreciate your introducing the people at the table with you to start.

INTRODUCTION OF WITNESSES

Dr. LENFANT. Thank you, Mr. Chairman.

Ms. Guerra, at the far left, is the Executive Officer of the Institute. Next to me here is Mr. James Wehling, Financial Management Officer of the Institute. On my right is Dr. Packard, who is the Associate Director of the Institute. You know Dr. Harold Varmus. And I don't know if you have met Mr. Beldon, who is here on behalf of the Department this morning.

OPENING STATEMENT

I'm very pleased to be here, Mr. Chairman, to report again on the National Heart, Lung and Blood Institute. Our research, as you know, is on the diseases of the heart, diseases of the circulation and diseases of the lung and blood diseases. Our research also is concerned with improving and maintaining the safety of the blood supply in the country. And then finally, we also have the responsibility for the National Center on Sleep Disorders Research.

Over the years we have had many successes. One of the most striking is the declining death rates from coronary heart disease and stroke, which is indicated on the chart over there. The red lines show a decline for stroke, approximately 60 percent between 1970 and 1993. And the green curve is for coronary heart disease, and that is a decline of approximately 50 percent.

In addition, because we see continuing decreases in the blood pressure, blood cholesterol levels, and smoking rates in the general population, we are confident that these trends will continue. I should say that we have seen similar remarkable decreases in the infant mortality rate in great part because of our ability today to treat respiratory distress syndrome, which is a very common lung complication of premature infants.

However, despite the successes, there are still many reasons for concerns. Each year, as Mr. Bonilla was pointing out during one of his comments, nearly half of the deaths in the United States are caused by heart disease. And of these, half are due to heart attack. Even more surprising is the fact that many of us may be disabled by heart diseases and other diseases for a long period of time.

And a case in point is congestive heart failure, which is a condition that has become extremely prevalent as the growing number of people survive heart attacks, which leaves them with significant damage to the heart muscle. And what I'm showing you here is the increase in the hospitalization rates from this condition that we are witnessing in the country today. That is certainly a very significant increase in hospitalization and morbidity of this condition, which is a significant burden on the health care system.

However, although our challenges appear daunting, the opportunities presented by research are many and very promising. And I would like to illustrate that with some examples. We reported not too long ago the results of a clinical trial of the drug hydroxyurea, which is the first effective treatment of sickle cell disease, by preventing the painful episodes which are one of the most significant complications of this condition. With this treatment, the occurrence of the painful episodes is reduced by approximately 50 percent, and so is the number of hospitalizations associated with this complication. In addition, the need for blood transfusions is also considerably reduced. So the results of this study showed a considerable increase in the well-being of these patients. But in addition, we are expecting to see a reduction in the cost of caring for these patients, with the reduction in hospitalization and the number of transfusions.

The second example is the Postmenopausal Estrogen/Progestin Intervention study, which actually was mentioned yesterday. This is the first study to show the beneficial effect of sex hormones on the risk factors of heart attack in women. The study, called PEPI, was concerned with women between the age of 45 and 65. I am pleased to say that last week, during a meeting at the American Heart Association, in San Antonio, it was reported that in effect, estrogen also prevents heart attack deaths in older women between 65 and 75. So we see here some very significant results for women at risk of heart attack.

The third example that I would like to mention is the development of a method to measure a blood enzyme which enables emergency room physicians to diagnose actual myocardial infarction. Now, that is very important, because approximately only one-third of the patients who enter the coronary care units in this country turn out to really have a heart attack. This method would allow us to diagnose who really is having a heart attack. The estimate for the cost of the "false alarms" is approximately $4 billion a year, and this cost, of course, by the dissemination of this new test, would be reduced. But perhaps more important is that the patients who really have a heart attack would be receiving a more rapid and better treatment.

It should be clear from all these examples that the key elements in cost savings is prevention, be it of primary diseases or of secondary complications of diseases. What may not be as obvious, however, but is critically important, is that none of these practical advances would have been possible without prior progress in our understanding of basic science.

To illustrate this point and to conclude my remarks, let me mention some of our work on blood stem cells, and tell you about the potential impact of this research. Now, stem cells are the precursors of all the blood cells, and are found either in bone marrow or in the circulating blood. To get them from the bone marrow is complex and presents some risk for the donors. To get them from the circulating blood is difficult and much work is needed to isolate and purify these cells.

It has been noted that another source of stem cells is from the blood of placentas. Placentas are tissues which are normally discarded after delivery. Preliminary work has shown quite well that we can now collect and bank the placental stem cells and that they have successfully been used for transplantation for the treatment of genetic and acquired disease, such as leukemia. They may also be used for gene therapy.

But the great benefit of this research is that placental stem cells have been shown to be very efficient and cost-effective means of providing compatible cells for transplant and in fact, there is some indication that they may engraft much better than stem cells coming from the bone marrow or from circulating blood cells. Much work needs to be done in this area, but here is an avenue of research which shows major potential, as well as significant cost benefits.

This concludes my remarks, Mr. Chairman, and I would be pleased to answer questions.

[The prepared statement and biography of Dr. Claude Lenfant follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Heart, Lung, and Blood Institute

I am pleased to address this committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI). As you may be aware, the NHLBI was established in 1948 as the National Heart Institute with the mandate to conduct research on diseases of the heart and circulation. During the 1970s, the Institute's scope was expanded to encompass lung and blood diseases and blood resources. Most recently, sleep disorders also became part of our mission. We address these issues through a comprehensive research program that includes basic and clinical investigations, population-based studies, and demonstration and education programs to move new research findings quickly into practice. These activities are carried out through extramural grants and contracts, research conducted on the Bethesda campus as part of the NHLBI intramural research program, and training and career development of investigators.

It is always satisfying to reflect upon the successes that this approach has wrought and, indeed, they have been remarkable. Age-adjusted coronary heart disease death rates declined 53 percent between 1970 and 1993, and rates for stroke declined 60 percent. Moreover, recent data indicating favorable decreases in blood pressures, serum cholesterol levels, and smoking rates in the American population support our expectation that these trends will continue. Infant mortality rates are now at a historic low, in large part because of improvements in our ability to treat and prevent respiratory distress syndrome, a common lung complication of prematurity. Life expectancy for people afflicted with inherited diseases, such as cystic fibrosis and sickle cell anemia, has soared as research has armed us with new skills to combat the devastating complications of these illnesses.

Nonetheless, there is still much reason for concern. As things stand, about half of the people in this room can ultimately expect to die of a cardiovascular, lung, or blood disease. Even more sobering is the fact that many of us may be disabled by one of these diseases for a long stretch of time--and spend a lot of money on medical care, as a result. Although we have made significant progress in averting deaths, success has been accompanied by a large increase in the population of Americans who suffer from chronic diseases. A case in point is congestive heart failure, a condition that has become extremely prevalent as growing numbers of people survive heart attacks, yet live on with significant damage to the heart muscle. Another is emphysema, a debilitating illness that is most commonly caused by cigarette smoking. These conditions not only make life miserable for the patient, but also result in huge expenditures for hospitalization, physician visits, drugs, and other forms of health care.

Although the challenges appear daunting, the opportunities presented by research are vast and promising. Several findings from recent studies illustrate the considerable potential of research to alleviate the human and financial burdens of disease. For example, the Institute just completed a clinical trial of the drug hydroxyurea, the first therapeutic agent for patients with sickle cell disease (SCD) to show promise of clinical efficacy without life-threatening toxicity. Hydroxyurea increases fetal hemoglobin, which is believed to reduce the frequency of "crises," the painful episodes that are the most common and disabling feature of SCD. The trial was halted ahead of schedule when interim analysis of data indicated that daily treatment reduced the frequency of crises and associated hospitalizations by more than 50 percent. Moreover, hydroxyurea therapy resulted in a significant decrease in acute chest syndrome, a life-threatening complication of SCD, and greatly reduced the need for blood transfusions.

The Postmenopausal Estrogen/Progestin Interventions (PEPI)--the first major clinical trial to examine the effects of sex hormones on heart disease risk factors in postmenopausal women--found that all four of the hormonal regimens tested produced increases in HDL ("good") cholesterol, and decreases in LDL ("bad") cholesterol and fibrinogen, a blood clotting factor predictive of stroke and heart attack. Although use of estrogen alone was associated with cell overgrowth in the uterine lining among study participants who had not had a hysterectomy, this potentially precancerous condition did not occur among women taking any of the three estrogen/progestin combinations. The results of the PEPI study provide scientifically based guidance for postmenopausal women and their physicians seeking safe hormonal regimens that will improve their heart disease risk factors.

The Lung Health Study (LHS) revealed that smoking cessation can reduce chances for development of chronic obstructive pulmonary disease (COPD) in high-risk smokers. The study recruited middle-aged men and women who had evidence of reduced lung function, but no clinical disease, and randomly assigned them to receive a smoking intervention, with or without an inhaled bronchodilator, or usual care. After 5 years of followup, participants in the smoking intervention program experienced significantly less loss of lung function than persons in the usual-care group. The LHS smoking cessation intervention, which combined state-of-the-art behavioral approaches with a nicotine replacement aid, realized a 5-year sustained quit rate (22 percent) higher than any ever reported in a major study. The study also showed that long-term use of a bronchodilator does not change the course of lung function decline in persons at the early stages of disease. Application of the LHS findings can be expected to have a significant impact on personal and financial costs associated with COPD.

A final example is the recent development of a new enzyme assay that enables emergency room physicians to diagnose or rule out acute heart attack within the first 6 hours after onset of symptoms, thereby reducing unnecessary admissions to coronary care units (CCUs). Currently, fewer than 30 percent of patients admitted to CCUs are subsequently found to have experienced a heart attack, and it is estimated that the cost of caring for "false alarms" in the CCU is $4 billion per year. The new test is also expected to save lives by facilitating rapid and accurate identification of patients who may benefit from clot-dissolving drugs.

It should be clear from these examples that a key element in cost savings is prevention--be it of primary disease, secondary complications of disease, or use of high-technology resources. What may not be as obvious, but is critically important, is that none of these practical advances would have been possible without prior progress in our understanding of basic science. If our public health objectives are to be met, we must continue to build a strong base of fundamental knowledge and capitalize upon the innovative opportunities provided by emerging basic science disciplines.

In this light, let me mention the Institute's recent initiatives to facilitate development of critical resources for molecular genetics research. The NHLBI Mammalian Genotyping Service was established in response to the need for a cost-effective, high-quality service to support projects that seek to identify the genetic determinants of cardiovascular, lung, and blood diseases. At present, genotypes typically are determined by investigators in their own laboratories using manual techniques--a process that is slow, redundant, and subject to error. We believe that existence of this new service will allow large populations and pedigrees to be analyzed reliably at reduced cost and will expedite current and future genetic studies of complex diseases.

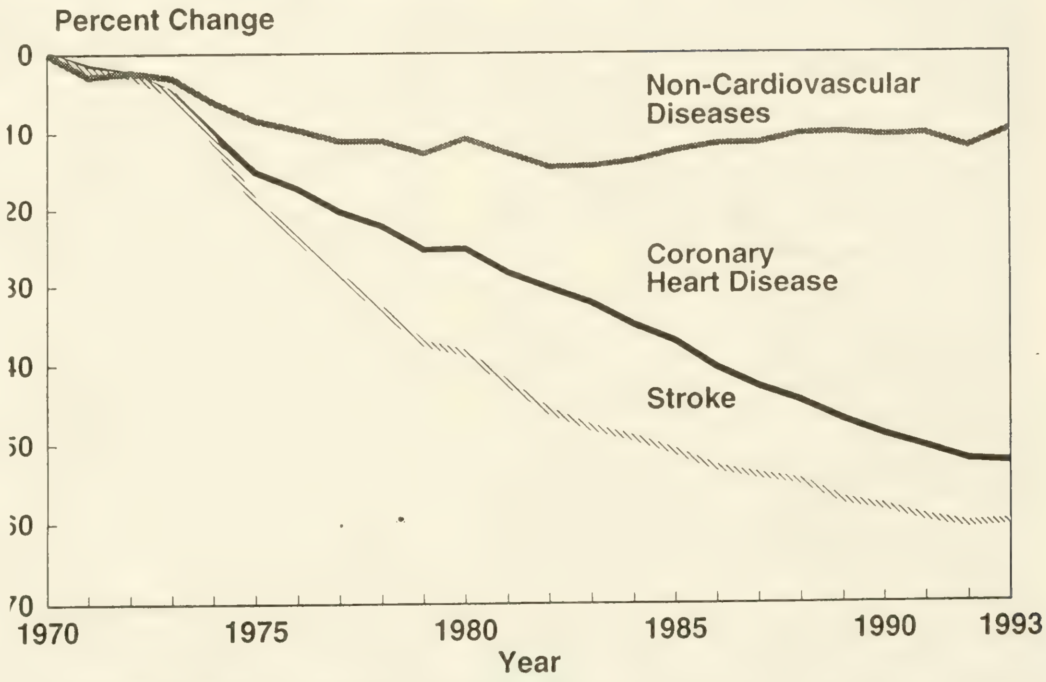
A second initiative is a collaborative effort of the NHLBI and 11 other NIH entities to develop a detailed genetic map of the rat genome and assemble a "library" of rat DNA fragments that can be used by investigators to identify specific genes. The rat is an important experimental model for studying many human diseases, such as hypertension, cancer, diabetes, and alcoholism, and a large body of knowledge about physiological mechanisms in the rat already exists. However, full utilization of the rat model for genetic studies has been hampered by the fact that individual investigators must resort to the laborious task of identifying genetic markers and mapping large chromosomal regions before they can attempt to locate the gene of interest. This new program will expedite timely and cost-effective development of essential resources necessary to develop the full potential of the rat as an experimental model.

Let me also comment on several new activities with respect to hematopoietic stem cells, the precursors of all blood cells. NHLBI-led advances in our ability to isolate and purify stem cells have placed the Institute in a strategic position to facilitate further development of this basic knowledge and its rapid transfer to the bedside. To accomplish this, we are implementing a new program, Specialized Centers of Research in Stem Cell Biology. We believe that stem cell therapies can be used to cure both inherited and acquired diseases and to provide life-long expression of normal genes. This effort capitalizes on a critical new opportunity to develop approaches to prevent and cure a wide variety of diseases.

Blood from placentas and severed umbilical cords--tissues that are normally discarded after delivery--has been shown to contain hematopoietic stem cells in sufficient quantities to reconstitute the bone marrow of some transplant recipients. The Institute is supporting a grant to determine whether a bank of frozen placental bloods is an efficient and cost-effective means of providing compatible cells for transplants. Such an approach offers the advantage of eliminating the delays and uncertainties that now complicate the acquisition of bone marrow from a sibling, other relative, or an unrelated donor. Several placental stem cell transplants, in which cells from the bank were used to reconstitute the marrow of leukemia patients, were performed during the past year with promising results. In view of this preliminary success, the Institute is considering developing a network of umbilical cord stem cell banks to facilitate exploration of this exciting new opportunity.

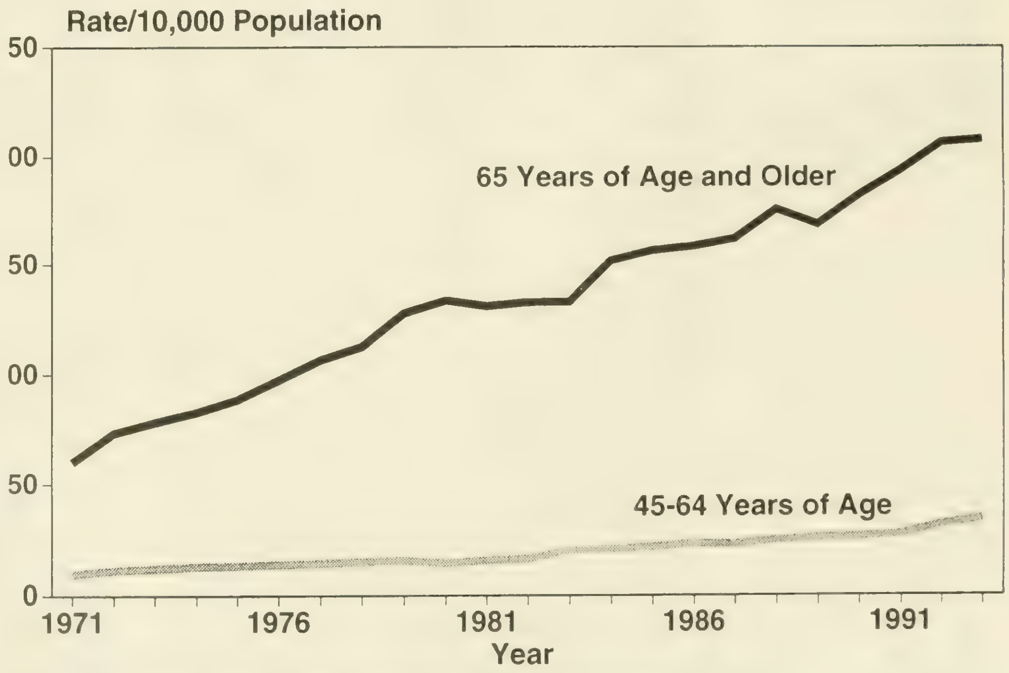
Mr. Chairman, the FY 1996 budget request for the NHLBI is $1,294,456,000. I would note that this figure includes $15.4 million for the National Bone Marrow Donor Program, which was formally transferred from the NHLBI to the Health Resources and Services Administration (HRSA) in November 1994. I would be pleased to answer any questions the committee may have.

Percent Decline in Age-Adjusted Mortality Rates Since 1970



Source: National Center for Health Statistics: Vital Statistics of the United States.

Hospitalization Rates for Heart Failure U.S., 1971-1992



Source: National Center for Health Statistics: National Hospital Discharge Survey.

February 1995

LENFANT, CLAUDE, M.D.
Director, National Heart, Lung,
and Blood Institute, NIH

October 12, 1928, Paris, France

Education: B.S., University of Rennes, France, 1948. M.D., University of Paris, France, 1956.

Professional History: 1957-1958, Research Fellow, University of Buffalo, New York. 1958-1959, Research Fellow, Columbia University, New York. 1959-1960, Assistant Professor of Physiology, University of Lille, France. 1961-1965, Clinical Instructor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1966-1967, Clinical Assistant Professor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1968-1971, Associate Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1970-1972, Acting Associate Director, Collaborative R&D Program, National Heart and Lung Institute, NIH. 1970-1972, Associate Director for Lung Programs, National Heart and Lung Institute, NIH. 1971-1972, Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1972-1980, Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH. 1981-1982, Associate Director for International Research, NIH. 1981-1982, Director, Fogarty International Center for Advanced Study in the Health Sciences, NIH. 1982-Present, Director, National Heart, Lung, and Blood Institute, NIH.

Professional Organizations: Association of American Physicians, American Society for Clinical Investigation, American Physiological Society, American Federation for Clinical Research, French Physiological Society, International Federation for Medical Electronics, American Society of Zoologists, Society for Experimental Medicine and Biology, Undersea Medical Society, New York Academy of Science.

Honors, Awards: Thesis Prize, University of Paris, France, 1956. Commendation Tohoku Medical Society, Sendai, Japan, 1973. Superior Service Honor Award, DHHS, 1974. Regents' Professor, University of California, Los Angeles, 1975. Testimonial Dinner, American Thoracic Society, 1979. Honorary Fellow, American College of Chest Physicians, 1979. Honorary Professor, National Yang-Ming Medical College Taipei, Taiwan, 1980. Honorary Professor, Universidad Peruana Cayetano Heredia, Lima, Peru, 1981. Senior Executive Service Performance Award, 1982. Elected

Institute of Medicine, National Academy of Sciences, 1983. American Heart Association Scientific Councils' "Distinguished Achievement Award," 1983. Senior Executive Service Performance Award, 1983. Honorary Fellow Council on Clinical Cardiology - American Heart Association, 1984. Senior Executive Service Performance Award, 1984. Forrest M. Bird Contributory Award, American Respiratory Therapy Foundation, 1985. Senior Executive Service Performance Award, 1985. Presidential Meritorious Executive Rank Award, 1987. Elected Honorary Member, Royal Society of Medicine, England, 1988. Honorary Doctor of Science, State University of New York, Buffalo, 1988. Elected Member, USSR Academy of Medical Sciences, 1988. Cystic Fibrosis Foundation "Breath of Life" Award, 1988. Elected Honorary Member, French Cardiology Society, 1989. Senior Executive Service Performance Award, 1989. Brotherhood Award - Association of Black Cardiologists, 1990. Appointed, Board of Governors, US-Israel Binational Science Foundation, 1990-1993, Senior Executive Service Performance Award, 1990. Presidential Distinguished Executive Rank Award, 1991. Elected Fellow, Royal College of Physicians (London, England), 1992. Senior Executive Service Performance Award, 1992. 1992 Federal Executive of the Year Award. Elected Member, French National Academy of Medicine, 1993. Surgeon General's Exemplary Award, 1993. Senior Executive Service Performance Award, 1993. Special Recognition Award - American Academy of Allergy and Immunology, 1994. Giovanni Lorenzini Foundation Prize for the Advancement of Biomedical Science, 1994. Senior Executive Association's Executive Excellence Award for Distinguished Executive Service, 1994. Senior Executive Service Performance Award, 1994.

Authorship, Editorship: Author or Co-Author of 200 scientific publications Served on Editorial Boards of: Am. Journal of Physiology; Journal of Applied Physiology; Respiratory Physiology; Am. Review of Respiratory Disease; Undersea Biomedical Research; Proceedings of Society for Experimental Biology and Medicine; Revue Francaise des Maladies Respiratories; Journal of Applied Physiology; Respiration, Environmental and Exercise Physiology; Am. Journal of Medicine; Continuing Education for Family Physicians; Executive Editor of 79 volumes for monograph series, "Lung Biology in Health and Disease."

Mr. PORTER. Thank you, Dr. Lenfant. You not only concluded your remarks, but you answered question seven on my list. [Laughter.]

BUDGET ALLOCATIONS TO NHLBI

I've asked you this in previous years, Dr. Lenfant. But I continue to be concerned that your Institute does not seem to fare as well as others in the competition for funds. This year, your non-AIDS budget request provides a 3.0 percent increase—below the biomedical research deflater—and less than that requested for some of the other Institutes.

Do you think that in a way you are a victim of your own success, that because of the impressive drop in the death rates for heart attack and stroke that your research program may appear to have somewhat less urgency compared to others?

Dr. LENFANT. Well, essentially, that's a qualified yes, in the sense that it is true that over the years we have made the decline in death rates quite visible. What perhaps we have not done, is emphasize the morbidity aspects of what we are talking about.

The point is that we have been very successful in reducing the death rate of these conditions. But we haven't been as successful in reducing the number of people who are getting these diseases. And therefore, because of the declining death rate and the lack of preventing the disease, the result is a much higher number of Americans who are now suffering from these conditions. That is something that we should address, and we have many scientific opportunities to address it very effectively.

LIFESTYLE FACTORS

Mr. PORTER. Isn't the problem of morbidity related in a major way to lifestyle, smoking, exercise, and the rest?

Dr. LENFANT. Many of the conditions that the Institute is concerned with are called chronic conditions. And many of these chronic conditions are the result of an interplay between our genetic makeup and the environment in which we live. And of course environment does include lifestyle, nutrition, exercise or lack of, weight control and what have you.

It is correct that the lifestyle influences a great deal the occurrence of the conditions that we are concerned with. And that is the reason why so many of our prevention problems are directed to changing lifestyles in individuals.

OBESITY

Mr. PORTER. One of the things we seem to find is the anomalous reaction that even when people know that things are not good for them, they seem to not give up bad habits, or even acquire bad habits. How do we deal with that phenomenon? For example, we know that overeating is a risk factor for heart disease, and yet apparently Americans are gaining weight and becoming less physically active than they were previously.

Dr. LENFANT. It is correct. But the point that we are making here relative to overweight in the United States is that it is of great concern to us who are interested in public health. Today, it is estimated that approximately 34 percent of American adults, and many children, I should say, are overweight. What is tragic is that this number increases instead of decreasing. It adds to all the other risk factors.

There is a lot of activity at the National Institutes of Health, some is reported by our Institute, some is reported by the Institute of Diabetes and Digestive Diseases and the Child Health Institute. It is a very, very difficult issue, obesity. Because as you pointed out accurately, people enjoy the things which eventually may lead to gaining excess weight, such as good food, perhaps lack of physical activities or watching too much TV and what have you. It is a real problem.

We are working very hard all together to try to address this problem. Whether we can be successful or not, I don't know. And I should point out another fact to you, Mr. Chairman, that in addition to this aspect that I've just discussed, there is also the point of view of some population groups in this country who live by their own cultures, and in some of these cultures to be overweight by other standards may not in fact be perceived as overweight. And so that is a real problem, because there is a great deal of sensitivity in the Nation, which requires a great deal of effort to be successful.

SMOKING

Mr. PORTER. If you walk into a restaurant in the United States today, you may see a couple of people smoking. If you walk into a restaurant in most places in Europe today, you have to cut through the smoke with a knife, because practically everybody smokes. Are there significant differences in the rates of mortality from heart disease in Europe as opposed to the United States, and if there aren't, what accounts for that?

Dr. LENFANT. Yes, there some major differences in the death rates between the United States and other countries. If you look at all of the countries in the world from which we can get data, the United States, as well as Scandinavian countries, Australia and New Zealand, are pretty much close to the top, where the death rates are the highest. If you go to Japan, it is one of the lowest. If you take the European countries, they are somewhere in the middle; it is a problem which raises enormous questions and as yet to which we have very few answers to explain these differences.

There is no question that dietary habits come into play. But we are aware of situations where the diet of a country, where the diet is not so good, relative to what we advocate in this country. And yet their death rate is much less than what it is in this country. I should say one of the best examples is France, where people refer to what is called the French paradox, where the diet is really not very good, with regard to what we are advocating here. And yet their death rate is approximately one-third of what it is here. Genetic determinants, lifestyles, stress, all kinds of factors come into play. I wish I could explain to you why it is so. I can't. But there is an awful lot of research that is going to try to identify all of them.

Mr. PORTER. So our death rate is higher than in European countries?

Dr. LENFANT. Indeed. Indeed.

But one thing that I would like to underscore, it may be the highest, but we are the country which makes the most progress to reduce the death rate, compared to all the western countries.

CONGESTIVE HEART FAILURE

Mr. PORTER. Could we talk a minute about congestive heart failure? The statistics that you showed show increasing amount of congestive heart failure. Could that be explained in part simply because people are living longer, they are otherwise more healthy and as they grow older, the heart grows weaker and unable to——

Dr. LENFANT. Yes, the fact that they live longer is certainly one factor. But the most important factor is that 25 years ago, middle aged men were having heart attacks and they would die from it. The death rate of heart attack 20, 30, years ago was mostly in the middle age bracket.

Today, it has been shifting, because we know how to treat these heart attacks, and these patients survive. They have one heart attack, two heart attacks, three heart attacks. And they are still alive. But in the process their heart is considerably weakened, and that is what leads to the development of congestive heart failure. They have a weak heart which is no longer able to accommodate the needs of the person.

Mr. PORTER. Could you explain exactly what congestive heart failure is, what is congested? When we talk about congestive heart failure, is it the lungs?

Dr. LENFANT. When you look at the human heart, it's something which is about as big as your fist, and all that is muscle. It's a very strong muscle. The heart is one of the strongest muscles that we have in the body. This muscle weakens after a number of heart attacks, or older age, or high blood pressure, for example.

See, the function of the heart is to move the blood into the vessels. Now, if for some reason there is resistance in the vessels, the heart has got to work harder to move the same amount of blood into these vessels. And that leads to the weakening of that muscle, which eventually cannot function properly.

Now, the word "congestive" here refers to the fact that because of that lack of proper action from the heart there is fluid accumulation into the lungs, fluid that remains in the tissue instead of being removed away, and that is really the process.

Mr. PORTER. I think it was Dr. Brown, one of our Nobel laureates, who spoke first here, mentioned lovastatin, is that correct?

Dr. LENFANT. Yes.

Mr. PORTER. As a real breakthrough with very little side effects. Would that presumably help a condition of congestive heart failure, where you're at least maintaining and perhaps even clearing the blood vessels?

Dr. LENFANT. It would not act on the congestive heart failure itself. What it would do is that, let's say a person has one heart attack. And if that person is treated with lovastatin, a drug which helps in recovering and may prevent further accumulations of lipids, the development of placque in the coronary arteries, you are going to keep that person from having a second heart attack or a third heart attack. And in so doing, you will prevent the development of the congestive heart failure.

So the answer to your question is yes, but not quite by the process that you indicated.

Mr. PORTER. I want to tell Mr. Miller that we on the subcommittee are privileged to get all this wonderful, free medical advice. It's one of the perks of service.

[Laughter.]

Mr. PORTER. Mr. Miller.

HEMOPHILIA

Mr. MILLER. Thank you.

I have a couple of questions, and a clarification. I'm a new Member of this committee, this is my third year, my second term. I remember my first time coming up here kind of lobbying as a layman, when I was a young father of a hemophiliac. And I remember one of the things we were lobbying for, and this was back in the early 1970s, a long time ago, was to put "Blood" in the name of this Institute. And I remember back then they were organizing hemophilia treatment centers.

I haven't really followed it that closely from my hometown area, but just generally. Where does hemophilia fit in the whole scheme of the Institute? I was just looking through this, and I haven't really seen it.

Dr. LENFANT. It is, as you know, an inherited disease, which is up to this point treated by a blood product. There are a number of complications or problems with this kind of process. The most significant one is that repeated infusions affect the immune system and may lead to reactions which are very serious. There are some complications that come from the hemophilia disease itself, which is excess bleeding, for example, internal bleeding, and that may lead to very serious problems.

The good news, however, with respect to hemophilia, is that because it is a genetic disease, there is a huge amount of work which is going on in our Institute, and in many institutions in the country, regarding the development of gene therapy, which basically would correct the genetic defect itself. The work is progressing well. I think we have reason to be hopeful. It is a very complex type of research, with lots of unknowns. It is a new type of research, and so it is difficult to predict when we might eventually be successful. But somehow, I am confident that we will have it.

Mr. MILLER. I remember when we were visiting NIH and Dr. Francis Collins was talking about how they're working on it in the genome project. But what is being done within your Institute on hemophilia? I was just using that illustration so I can understand the bigger picture.

Dr. LENFANT. Sure. We are doing some work within our intramural program. I'm sorry you didn't see that when you were at NIH, where we work on the development of the vectors for inserting the gene into the patients, and doing some work on animal models. That is done within our Institute. In fact, in cooperation with our Genome Center.

In addition to that, we are supporting quite a bit of work in a number of other institutions in this country where investigators are really working along the same lines and in cooperation with our own investigators.

Mr. MILLER. Is this type of research addressed in other institutes at the National Institutes of Health?

Dr. VARMUS. A majority of the hemophilia research goes on through Dr. Lenfant's Institute. But there are other places where the research goes on.

For example, at biotech companies, there is a tremendous interest in the production of factors 8 and factors 9, which can be used therapeutically in place of transfusions of plasma as a means of controlling hemophilia. So it's impossible to make these factors that are missing in the blood of the patients who have hemophilia, the fact that it's been made in a simpler system.

Mr. MILLER. Right. Unfortunately, our son was born after development of the concentrate and change in the treatment. And I know there are a lot of things happening; however, I'm not into the technical aspect. So there's not a huge amount really being done within the Institute?

Dr. LENFANT. Within our Institute, it's—I cannot tell you what amount of money is being spent——

Mr. MILLER. Could you send me a letter to that effect, about what is being done on hemophilia?

Dr. LENFANT. All together, looking at the intramural elements and extramural elements of the research, we are supporting approximately $16,000,000 in hemophilia research.

MINORITY RESEARCH

Mr. MILLER. Let me switch to another question, and maybe Dr. Varmus could answer this, too. I saw this yesterday in the report, and I saw it the day we were visiting out at NIH, the role of minority research. I see it's a separate line item in the budget. Explain to me, I know this is not just your Institute, but I guess yesterday there was a book given to us about all the minority programs. Explain to me what the minority program is in research, so I get a better understanding.

Dr. VARMUS. Let me just say a few words about that. First of all, much of the research that we do is not specific to minorities. So a great deal of research applies to minority populations. You heard yesterday some discussion of our determination to include minorities and women in our clinical trials, and of course, all our basic research applies to minorities.

But we recognize at NIH that research on the health of women and minorities in particular has been neglected in some areas over the years. In efforts to compensate for that deficiency and also in recognition that minorities do have a disparity in health status in this country, we have tried to place special emphasis on certain programs to repair some of those deficiencies.

We do the analyses in two ways. One is to look at the budgets across all the Institutes, and to ask how much is being spent specifically on minority populations. For example, in Dr. Lenfant's Institute, we know that hypertension is a disease which preferentially affects African Americans. We attribute some of those research dollars as minority research.

To try to further bolster our support of research on disorders that affect minorities, we established some years ago, before I came to NIH, the Office of Research on Minority Health. That office, which is directed by Dr. John Ruffin, who will be here when the Office of the Director presents to you next Thursday, is devoted to spending money in several ways to improve minority health.

There are minority training programs to ensure influx of minority scientists into NIH research efforts. There is money spent through the Minority Health Initiative, totalling about $60,000,000. This is a fairly small fraction of our total budget, and it is money that's used to co-fund or supplement grant applications that have already received a high priority score from the Institutes. Although there is research activity supported by that Office, the Office is used to promote minority initiatives in other Institutes.

Mr. MILLER. For example, I saw there was $60,000 more requested for minority research, and there is something like a $2,500,000 line item in the budget.

Dr. VARMUS. It's a $5,000,000 increase for this year.

Mr. MILLER. For the year. I mean, just in this Institute, is that right?

Dr. VARMUS. The NIH in general is applying an additional $5,000,000 over the previous level of support for the Minority Health Initiative.

Mr. MILLER. For example, it shows here, minority biomedical research is——

Dr. VARMUS. Yes, I mean——

Mr. MILLER. Pardon?

Dr. LENFANT. You are talking about my Institute?

Mr. MILLER. Yes.

Dr. LENFANT. That particular item is a program to support research in minority institutions, that's what it is.

Mr. MILLER. So this would in effect be a setaside, an affirmative action issue? I don't want to debate the issue, I'm just saying this is——

Dr. LENFANT. It is a setaside for research being done in minority institutions.

Mr. MILLER. When we have the——

MINORITY HEALTH DISPARITIES

Dr. LENFANT. If I may say something, Mr. Miller, which is a very important point. As Dr. Varmus underscored, there are some health issues which are specific to minorities. One of them is sickle cell disease, which I mentioned earlier. Or where you have a very significant disparity between minority and non-minorities, such as high blood pressure or coronary heart disease.

I showed you earlier the decline in death rates from coronary heart disease for non-minorities in this country is approximately 3.2 percent per year. In minorities, it's only 2.2 percent per year. So we have to understand this disparity.

So how can you do that? There is one key factor which is what this program you mentioned addresses. You have to find investigators, minority investigators, who are going to work with minority populations, in order to address this issue. If a non-minority physician, goes and works on minority populations, you can do something, but it's not as good as if the investigator is a minority physician.

And so the purpose of this program is to develop a cadre of investigators, minority investigators, who do their own research and can address this problem in a much more effective fashion than a non-minority scientist would be able to do it.

Mr. MILLER. I assume that when we talk with the Office of the Director we'll have more of an explanation and clarification of what exactly the whole minority setasides and such are.

Dr. VARMUS. Yes. We can give you more information. I caution you, though, that the minority programs are not all directed to minority institutions or to minority scientists. In many instances, the so-called minority programs are carried out by non-minority scientists.

Mr. MILLER. Yes, I'm not in a philosophical discussion now, I'm just trying to——

Dr. VARMUS. We can provide you with much more detailed information.

[The information follows:]

National Institutes of Health

The NIH supports the conduct of research and research training to improve the health of all Americans. Minority students and scientists are encouraged to participate in all of the NIH biomedical research and training programs. In addition, some programs have been created to promote the participation of underserved minorities and these have significantly increased over the last few years, often in conjunction with our efforts to work with Historically Black Colleges and Universities (HBCUs) across the nation. In the 1970s, President Nixon signed an Executive Order at Howard University dedicating the resources of the Federal government to support HBCUs. Through the efforts of Dr. Geraldine Woods and Congressman Louis Stokes, the Congress appropriated funds to begin the first programs at NIH identifying the needs of minorities; the Minority Access to Research Careers (MARC) program and the Minority Biomedical Research Support (MBRS) program. The purposes were, and are today, to train underrepresented minority students in the sciences and encourage them to enter biomedical research careers (MARC), and to provide infrastructure support to HBCUs and other educational institutions with significant minority student enrollments, so they may conduct research activities (MBRS).

Another program to provide major infrastructure support for research activities at Ph.D. granting HBCUs was mandated by Congressional action, the Research Centers at Minority Institutions (RCMI) program. More recently, in order to produce larger numbers of well-trained minority scientists, the NIH launched a minority supplements program where grant funds to NIH supported research scientists may be supplemented in order to add a minority person at any level of training from high school through faculty. The purpose in the MBRS, RCMI and Supplements program is to increase the number of scientists in the workforce in the 21st century and to increase the number of scientists in the future with special interests in the specific health of minority groups.

Many of the NIH minority programs funded through a grant mechanism are not exclusively for minority participants. For research training, the mechanism of award is an institutional grant award where the institution (college or university) determines the eligibility of the participants and may favor the selection of underserved minorities for that program. Award decisions are not based on "set asides" but are made based on the merit of the program as determined by peer review of applications submitted. Many of these programs are supported by line item appropriations in the NIH budget, but awards are made only when the high quality of an application is demonstrated.

It should also be noted that the research targeted at the health problems of minorities is also beneficial to the health problems of all Americans, since there are no diseases exclusive to any one ethnic or racial group. Thus, it is not possible to list research grants, research contracts or cooperative agreements which only study minority health issues.

The term "program" within NIH has many meanings. First, there are extramural programs and intramural programs within nearly all Institutes. The extramural program carries out its mission through grants, contracts, and cooperative agreements that are awarded competitively. The intramural program conducts its business using contracts and purchase orders. Each extramural award that is made must be assigned an activity code so that all grants of the same type have the same code. Therefore, the extramural programs of NIH are described by the codes listed in the NIH computer-based information system. Beyond this broad use of the word "program," there is also the tendency to use this term readily as an umbrella term under which are lumped several activities; for example, one may see the phrase "program initiative." In other words, the term "program" is not consistently defined or used within NIH or perhaps even the Department. Often, special efforts or even individual projects are labeled "programs." In addition, the term "minority" appears in many titles of projects, activities or programs, etc., when the design of the effort is slanted primarily, but not exclusively, for minorities.

Many of the "programs" are not in fact programs with an activity code, but are efforts announced as part of a larger activity, whether it be intramural or extramural, which is not a designated minority effort. Those "programs" sent forward from the NIH in budget documents are designed primarily for individuals as beneficiaries and in many cases, those individuals are minorities. For example, minority predoctoral fellowships may be in the same category as all predoctoral fellowship programs of an Institute and therefore not qualify as an overall targeted minority program.

Mr. MILLER. Okay. Great. Thank you very much.

Thank you, Mr. Chairman.

COMPETING GRANTS

Mr. PORTER. Dr. Lenfant, your budget indicates that your Institute will experience a significant drop in the number of new and competing grants awarded in 1996, a decrease of more than 20 percent. The total number of grants awarded would remain about the same. Is this an outcome of the natural fluctuation of grants cycling in and out of the system, or is something more complex happening?

Dr. LENFANT. It's a result of the fluctuation and the relative distribution between competing and non-competing grants. As you point out, the total number will remain approximately the same. And the reason why the competing number is decreasing from 690 to 576 is because the non-competing number increases by the same number.

GRAFT VERSUS HOST DISEASE

Mr. PORTER. Your budget justification indicates that about half of the unrelated bone marrow transplant recipients experience life-threatening graft versus host disease.

Dr. LENFANT. That's right.

Mr. PORTER. Due to the good work of our colleague, Congressman Bill Young, who's not here this morning, we are all enthusiastic about this form of therapy. But does this statistic imply that the transplants from unrelated donors work only 50 percent of the time?

Dr. LENFANT. No. Not all the graft versus host disease leads to a negative outcome. It is a complication. It is a very serious one, which may lead to the rejection of the graft, but not in all instances. All in all, I believe that the success of these transplantations within a three or four year period is approximately 60 percent for good risk patients.

What I mentioned earlier about the stem cells, the placental stem cells, may be a way to address this problem. What I was trying to say earlier is that the transplantations which have been performed using placental stem cells have led to much less graft versus host disease and therefore, if this complication is not present you can expect that there will be success.

Mr. PORTER. You still might have a problem using stem cells, but it would be much less likely?

Dr. LENFANT. That's correct. Now, the Institute is conducting a study which consists in removing the T-cells from the blood, the cells that you are going to transplant. There is some evidence that removing these T-cells may indeed reduce the complication of the graft versus host disease, which is a very serious problem. It's a very serious problem.

SICKLE CELL DISEASE

Mr. PORTER. We were pleased with the news of the first clinical therapy for sickle cell disease. Will this treatment result in a significant quality of life improvement for a substantial share of those afflicted with the disease?

Dr. LENFANT. Absolutely, Mr. Chairman. One of the most excruciating complications of sickle cell disease are these painful episodes. And you really have to see one to know what it is. I mean, it's a terrible sight to see. What this drug does is to prevent the occurrence of these painful episodes in many patients. Not all of the episodes, but many of them. A patient who is not treated may have two, three, maybe four such episodes a year. With this treatment, the number is reduced by about half. As I was pointing out earlier, one of the important aspects of that is that when one patient has a painful episode, that patient must go to the hospital to be treated. That now is no longer the case, and therefore the cost savings for these patients and their well being, as well as their opportunity to work, is considerable.

MAPPING THE RAT GENOME

Mr. PORTER. Your written statement indicates you and other Institutes are starting an initiative to map the rat genome. Why does the rat happen to be such a good model for cardiovascular disease, and why hasn't the rat genome been a component of the genome project from the start?

Dr. LENFANT. Well, let me address the first question first. First of all, to address many of these diseases, cardiovascular or what have you, you need to have an animal model. We know a lot about the genome of the mouse. Unfortunately, because the mouse is very small, it's very difficult to study the physiology of this animal.

In contrast, rats, are fairly large animals; their physiology is very well known; and you can equip these animals with all kinds of instruments, which allow you to measure whatever physiological variables you are interested in. But the rat genome is not very well known. So the project here is to study the genome of the rat because we have established that it will cost less money to develop the genome of the rat than to develop a process to measure the physiology and all kinds of physiological variables in the mouse.

Now, your second question as to why the Genome Center hasn't mapped the rat, the fact of the matter is that the Genome Center is going to run this project, and are going to be responsible for it. The goal of our Institute has been to, in a way, create the impetus, because the rat is such an important animal model for the studies of these diseases that we are discussing. And then many of the Institutes interested in the project, all agree that the Genome Center, which has an expertise that we do not have, is going to be responsible for it. In fact, this project is really a wonderful example of the cooperation between the various Institutes of NIH; 12 or 13 institutes are all supporting this project.

Mr. PORTER. Why hasn't it been a component from the beginning?

Dr. LENFANT. Well, I think the reason is that the Genome Center was primarily interested in the development of the genomic map of the human. And that was primarily their role. And we came to them, and we said, we have to do some studies on cardiovascular diseases using the rat as an animal model, and that's how we got them interested in this.

Dr. VARMUS. If I could, sir, the model that was chosen was the mouse initially, because of the ease of genetic manipulation in the mouse. And the rat presents many physiological advantages and it is now being added on, and we think not at too late a date.

Mr. PORTER. I think we discussed, Dr. Varmus, how close the mouse is to humans. Is it——

Dr. VARMUS. The rat and the mouse are about——

Mr. PORTER. The rat and the mouse must be somewhat akin?

Dr. VARMUS. They're about 10 million years separated in evolution. The comparison of the mouse, the rat and the human genomes is going to be extremely useful. It's already proved to be useful, because there is a preliminary map of the rat that was recently published as a result of work done by grantees of Dr. Lenfant's Institute and grantees of the genome project.

SLEEP DISORDERS RESEARCH

Mr. PORTER. All right. As you know, I've been interested for some time in the establishment of the National Center for Sleep Disorders Research. Can you review for me its activities in its first year and how it is targeting its resources. Specifically, how does it divide its focus between education and prevention activities and research, and what is the status of the appointment of a permanent director for the Center?

Dr. LENFANT. Let me address this last aspect of the program first. We have now appointed a permanent director of the Center. He does not spend all of his time on this activity, but he is a permanent director. The reason why he does not spend all of his time is that the Center is in its development phase, and he and we know there is not enough for him to be there all the time.

Programmatically, the Center has been quite successful, certainly within the Institute. Let me just give some figures. In 1992, our commitment was approximately $8,800,000 for sleep research. In 1995, that is this year, it is $15,500,000, and we expect that we'll reach $17,000,000 or $18,000,000 next year.

The justification for this increase is the initiation of a number of research programs which has been done by the NHLBI. In addition to that, as you know, there are several Institutes at NIH which are interested in research on sleep disorders, for example, my colleagues in the Neurology, the Mental Health, and the Aging Institutes.

We, the Center have a coordinating function. The director of the Center works with all of our colleagues in the other Institutes to foster their own activities as well as common activities. An example of that is that there is going to be a very significant workshop to assess where we are in sleep disorders, which is sponsored by all of the Institutes. There is also a program announcement which has been issued and sponsored by all of the Institutes.

So the research is going well. We are confident that we are on the right track. Further, one of the responsibilities that we have is—well, we were mandated by the legislation—to create an Advisory Board to develop a research plan for the Director of NIH, as well as the Director of the Heart, Lung and Blood Institute. That Board is working on the development of that research plan, and my expectation is that it should be ready within six to nine months.

Your last question had to do about education programs. We have initiated our own education programs; such as public service announcements, and we have what we call the "Health Beat," which is given on the radio several times a day, or whenever appropriate. We have worked with the Department of Transportation to initiate a campaign which is a Drive Alert, Stay Alive, or Stay Alive, Drive Alert, I mix up the order of these two things. We also initiated, and completed, actually, an effort with the National Institute on Child Health and Human Development on sudden infant death. As you know, we encourage parents to leave their infants lying in a supine position rather than their side. And that effort of public, as well as professional education, has been very, very successful.

LIFESTYLE AND HEALTH

Mr. PORTER. Just a final thought before I go to vote. We talked earlier about finding out what is a good lifestyle to promote good health in human beings, and even knowing that, not following it. And when we had the Nobel laureates here, a question was asked, what would be your two highest priorities if you could only get two. And a number of them put mental health or research on behavior or the brain as a high priority. Do you think that that's maybe what they were thinking about when they answered the question?

Dr. LENFANT. Well, I don't know what they were thinking about. The issue of lifestyle is an extraordinarily difficult issue. Because convincing people that what they should do different from what they do, presumably because they enjoy it, is very difficult.

Mr. PORTER. Well, it was a bit of a facetious question.

I'm going now to vote. Mr. Bonilla.

CARDIOVASCULAR DISEASE DEATHS

Mr. BONILLA [presiding]. Thank you, Chairman. I have voted.

Good morning, Dr. Lenfant. Good to see you again.

Dr. LENFANT. Good morning, sir.

Mr. BONILLA. Let me start off with a few statistics. In your testimony that I've reviewed, it says that about half the people in this room can ultimately expect to die of cardiovascular, lung or blood disease. Members of this subcommittee come from states that are in the top ten or so in total cardiovascular diseases, heart attack and stroke deaths.

Just briefly, total cardiovascular diseases: Mississippi is number one, Oklahoma number ten, Arkansas number eleven—I was hoping Mr. Dickey would be here for this, to hear that—New York, number twelve. Heart attack: New York is number one, Oklahoma number two, Arkansas number five, Ohio number nine. Stroke: Arkansas is number two again and Mississippi number three. And this subcommittee only comes from eleven different states.

Those figures tell me two things: one, that cardiovascular diseases are still the number one cause of death in this country, and two, this subcommittee should be lucky that Mr. Dickey is not dead.

[Laughter.]

We kid a lot. [Laughter.]

I also understand that about 80 percent of patients with diabetes die from diseases of the heart or diseases of the blood vessels such as stroke. Why is that? What's the link?

Dr. LENFANT. Well, first of all, the diabetes itself is a risk factor for heart disease because of the impact of this condition on the blood vessels. Now, the blood vessels of course are very much involved in stroke, as well as in coronary artery diseases. And the issue here is that diabetics have a tendency to develop what we call plaque and atherosclerosis much more than a non-diabetic subject. And that is the link between diabetes and these conditions.

Mr. BONILLA. And it's all blood related, correct? The link is just the blood problem that develops?

Dr. LENFANT. Yes, yes.

RESEARCH IN TEXAS

Mr. BONILLA. I understand that you recently went to Tyler, Texas—which is known for its roses, in Texas—to visit with the Health Science Center there at Tyler. What did you bring back with you from the trip? What did you learn while you were there?

Dr. LENFANT. I was, I must say, very positively impressed by what I saw there. I was not aware, because it is not a full medical school, and they simply call themselves a Health Center. It's going to be a post-graduate school, where they complete their medical training. I was very impressed to see the research that's going on, and how that research has been increasing over the years. As you know, most of the research is in the pulmonary area, because they were at one time, I believe, a TB hospital, which developed into a more general hospital. At the present time, they are also working to develop a cardiovascular research program.

So I was very, I must say, positively impressed. I saw much more than what I expected to see. It so happens that I've known Dr. Hurst for quite some time. Dr. Hurst, as you know, is the director of the Center. And it also so happens that some of the people who work there I have known for a number of years. In fact, one of them used to be, I would say, a trainee of mine. So I found it a very interesting, and I think helpful visit.

Mr. BONILLA. There is so much to the University of Texas health research system, whether it's in Houston or San Antonio, or in Tyler. I really feel fortunate that you were down there, and hope that you can come back again at some point when you cross the country. Maybe you can swoop down a little bit and come through our state one more time.

Dr. LENFANT. We have quite a bit of support in the university in your own city.

Mr. BONILLA. Absolutely.

Dr. LENFANT. And we have support, actually, from each of our programs there. Perhaps the most significant is the one with Dr. Wood, where they're working on asthma.

Mr. BONILLA. And there are so many areas, whether it's diabetes research or asthma or podiatry. All of these areas have tremendous programs down in south Texas. And just because they're concentrated in one area, I know you're not deceived by this, but they really fan out for hundreds of miles and cover huge masses of areas and encompass so many different ethnic groups and economic groups as well. So I think it provides a tremendous cross-section. It covers a huge cross-section in this country.

Dr. LENFANT. And of course, there are a number of population groups, there are some American Indians, there are some Hispanic Americans, there are some African Americans and of course some Caucasians. And that enables us to make some very interesting comparisons, which are very valuable. Actually, what you learn from one group is relative to another group and vice versa. So the participation that we can get there in the community that is so diverse is very helpful.

COMPREHENSIVE HEART, LUNG, AND BLOOD DISEASES CENTER

Mr. BONILLA. I guess a question related to the Tyler campus, last year we talked about a comprehensive heart center. Language was included in both the House and Senate reports about the center, which as you know, we were involved in on this committee. And I see in your budget justification that it states, "The NHLBI is currently considering the utility and feasibility of establishing a comprehensive research and demonstration center for heart, blood vessel, lung and blood diseases. The director will be prepared to testify on this topic at the appropriations hearings."

Dr. Lenfant, what can you tell us about the utility and feasibility of a center at this time?

Dr. LENFANT. Well, this is a very interesting question, and it is true that since we saw this in the report last year, the Institute and I have spent considerable time thinking about this issue. Let me say at the outset that we believe that comprehensive centers are a very useful, important instrument to address health-related issues, as well as to benefit the people who are in the community where the center is. The best example I could give you of that are the sickle cell disease centers. You may know that by legislation we are bound to support ten such centers. And we do know for a fact that they have considerable impact on the communities where they are.

We have had in the past, about 25 years ago, some comprehensive centers on heart and lung diseases. We were obliged to discontinue them because the problem was that, they are very expensive on the one hand, and we felt that we had other mechanisms of support which would allow us to do pretty much the same thing. It may not be under the same umbrella, but adding pieces here and there we could do the same thing.

Our position, which I would like to share with you, Mr. Bonilla, and hope that you will accept it, is that within the constraints that we have today, I do not believe that one center or a network of centers would be the best way for us to achieve our goals. We can achieve our goal in a decent fashion without this huge instrument of support, which again is very expensive and which at this point in time, with all the priorities that we have, really cannot be afforded.

But again, I believe, and in fact that is what Tyler is doing, that they can achieve in one institution, one community, what a medical center can achieve by taking advantage of all the less expensive mechanisms of support which are available. Tyler is very successful in that, they have programs of education, they have programs of very basic research. They are lacking a little bit in the clinical research, but I think that they are thinking about it. I hear from Dr. Hurst that they want to bring new people to do that kind of research and develop this kind of activity.

Mr. BONILLA. Yes, but the research is at the University, and they see an advantage to having the center there. Did they not when you were there?

Dr. LENFANT. Well, yes.

Mr. BONILLA. The implication is that perhaps they were not——

Dr. LENFANT. There is an advantage in doing that, because so to speak, you receive a lump sum of money, which is fairly sizeable. There is a distinct advantage to that over having to compete for several instruments. But if you put all the money in one place without specific competition, it really creates imbalance in the research portfolio, which has limitations as we view it today.

RISK FACTORS

Mr. BONILLA. I hope this is still in the preliminary stages and that we'll be able to talk more extensively about the advantages of having it there, and I certainly understand the reservations you're expressing. But we want to keep pressing forward. So we'll do that.

I'm going to move to a different area now, Dr. Lenfant. I was fascinated by a chart I received when we all toured the NIH recently. And you were a great host, as were your fellow doctors, that day we spent there in January. The chart shows that being overweight, or overweight with hypertension, or overweight with hypertension and high cholesterol, the person has a higher prevalence of risk factors for cardiovascular problems than smoking. Could you put that chart in the record, and could you explain the significance of risk factors among the two groups, obesity versus smoking?

[The information follows:]

PREVALENCE (PERCENT) OF RISK FACTORS—UNITED STATES, 1988–91

	Total	Men	Women
High total cholestrol	22.4	21.0	23.2
Hypertension	27.1	28.6	25.2
Overweight	35.2	33.1	37.0
Cigarette smoking	30.3	33.7	27.1
High chol+Hypertension	9.5	8.1	10.5
High chol+Overweight	9.4	8.3	10.3
High chol+Smoking	6.1	6.9	5.4
Hypertension+Overweight	13.6	13.7	13.3
Hypertension+Smoking	8.5	8.4	8.7
High chol+HPT+Overweight	4.8	4.1	5.3
High chol+HPT+Smoking	2.0	2.5	1.5
High chol+Overwt+Smoking	2.0	2.0	2.0
Hypertension+Overwt+Smoking	2.5	2.7	2.4
All four risk factors	0.8	0.9	0.7

Note.—Age-adjusted to 1990 population aged 25+—NHANES III.

Dr. LENFANT. Yes, well, they are both very important risk factors. There is no question that the smoking is probably—let me backtrack and just make a comment, so I can more specifically answer your question.

One of the things that we would love to say is which risk factor is more important among all the risk factors that exist. Well, this is a very difficult thing to do, and it's more difficult to do it when talking about individuals. You know, you have people who are 80 years old and have been smoking for 60 years, and they feel perfectly fine. So in that case, for smoking, it would not be a significant risk factor.

Now, looking at the population as a whole, which is your question, the scientific community believes that smoking is probably the most important risk factor. Obesity is also a very important risk factor.

And one of the reasons you may be interested to hear why I say it may not be as important for some individuals, is that when you compare Hispanic Americans with Caucasians, you see that Hispanic Americans are blessed by having much less heart disease than Caucasians, or Blacks, for that matter. Now, they don't smoke as much. Smoking in Hispanic Americans is much less than in Blacks or Caucasians. But in contrast, there is a tendency to have more obesity in Hispanic Americans. And so you see, that shows you the difference between these risk factors.

Our public health approach, and I insist our public health approach, is to address collectively all of these risk factors: smoking, overweight, blood pressure. Incidentally, there is a close correlation between overweight and blood pressure. Approximately, I think it's 45 percent, almost half of overweight people have high blood pressure. And of course, elevated blood cholesterol is also a very important risk factor.

Mr. BONILLA. The reason I talk about this, Dr. Lenfant, I know I brought it up during our visit to the NIH, is because I'm obviously not a doctor. But I see so many people that are killing themselves eating terrible foods, and I'm sure they're hurting themselves by smoking, and I don't advocate that anyone smoke.

But it seems to me that all of the attention, or the majority of the attention, is always focused on smoking when people are stuffing their face every day, killing themselves. And there's always talk of regulating restaurants or second-hand smoke. And yet nobody comes up with ideas of regulating, and not that I advocate this, regulating what kind of food you serve in a restaurant—you can only have so many strips of bacon in the morning. [Laughter.]

And that's the reason I was referring to this chart. Because I think it's not a controversial or sexy subject to bring up a lot, people focus more attention on smoking. I've said on this committee before that I just have a strong sense of fairness, and wonder why more attention is not addressed toward obesity versus tobacco.

Dr. LENFANT. There is an awful lot of attention which is given to obesity. Maybe it hasn't been picked up by the media as much as smoking.

DIET AND HEART DISEASE

Mr. BONILLA. Well, you're right, Dr. Lenfant, and I know that physicians in general always address it. And I'm not addressing my criticism toward that. I know that it is the media that chooses selectively to pick up on these things.

Dr. LENFANT. On the front page of the Post today there's an interesting article, where actually they refer to the cafeteria in the National Institutes of Health——

[Laughter.]

Dr. LENFANT [continuing]. Where they say that they don't use fat to cook their vegetables. You may be interested to know that four or five years ago, I myself dressed as a cook and went to work in the cafeteria at the NIH to observe their cooking habits.

Dr. VARMUS. I think we need you back there. [Laughter.]

From this morning's article. But there has been a reduction in the percentage of dietary fat over the last several years. I think it may be in response to what has been an adequate media campaign to reduce fat in diet.

Mr. BONILLA. You say there's been a reduction in dietary fat? Then why are we seeing all these reports now that people aren't paying any attention to that? I mean, what is it? We saw the Time magazine article a few months ago that says we're going back the wrong direction again. Is that true?

Dr. VARMUS. Well, overweight is not necessarily related to the amount of fat in the diet.

Dr. LENFANT. I think the biggest problem that we witness today is the lack of exercise. People in this country, you know, during the 1970s and 1980s, went jogging and were doing exercise. But now one of the problems, the level of activity, physical fitness is less than it should be.

But you've got to keep on trying, and that's what we do. Because these are very, very difficult problems to address.

VASCULAR STENT RESEARCH

Mr. BONILLA. A couple of final questions, Dr. Lenfant. Could you tell us the significance of the vascular stent that was discovered by biomedical engineers at the University of Texas at Arlington in UT's Southwest Medical Center in Dallas?

Dr. LENFANT. I would like to perhaps respond on that for the record. There is so much work that is going on, I——

Mr. BONILLA. It's at Southwestern at Dallas.

Dr. LENFANT. I will put that in the record.

Mr. BONILLA. I would appreciate that.

[The information follows:]

VASCULAR STENT

In FY 1994, the University of Texas received one of the three grants funded under a new NHLBI initiative entitled "Genetically Enhanced Cardiovascular Implants." The estimated total cost of the grant is approximately $1.1 million for the 4 year funding period.

The University of Texas bioengineers and scientists are attempting to prevent the reocclusion of coronary arteries following balloon angioplasty by developing a vascular stent loaded with a genetic cocktail to enhance its biocompatibility and maintain patency of the artery. Without such a device, 30–40 percent of the approximately 300,000 patients who are annually subjected to balloon angioplasty will have to undergo a second procedure when their coronary artery closes again. The proposed device could favorably impact the success of these procedures and greatly enhance the quality of life of patients receiving angioplasty. The process used to genetically enhance the stent would be directly applicable to vascular grafts and other cardiovascular implants.

Mr. BONILLA. My understanding is that there is a $1,000,000 grant from NIH to fund this research. We just want to confirm that.

Dr. LENFANT. Well, I'm glad to know that they have this grant, most likely from us, but you know, we have almost 3,000 grants, so I don't have them all in my head. It's too small for that.

Mr. BONILLA. Sure, I understand. It's like when people come into my office to ask me about H.R. 3491. [Laughter.]

I don't have them all in my head, either.

Well, at this point, we'd like to thank you for appearing for us today, and it's good to see you again, Dr. Varmus. And we look forward to visiting with you again very soon. And we're going to now recess.

There may be additional questions for the record, you'll be hearing from us on that. I thank you very much for appearing.

Dr. LENFANT. Thank you, sir.

[Recess.]

[The following questions were submitted to be answered for the record:]

STREAMLINING

Mr. Porter: Your justification described the committee you appointed identified by the acronym, "BOLD," which made far-reaching recommendations to streamline and reorganize your Institute. Can you outline the major changes you have undertaken to implement the committee's recommendations?

Dr. Lenfant: The NHLBI has implemented the recommendations mentioned in the justification as follows:

Five Extramural Divisions and three Offices have been reorganized to consolidate and/or eliminate branches and sections, which we determined to be unnecessary administrative layers or inhibited organizational flexibility. The changes in organizational structure were effective October 1, 1994. These reorganizations eliminated 42 formal organization entities, and changed the supervisor-to-employee ratio from 1:4 to 1:11. Further organizational changes are under consideration which include a consolidation of procurement and administrative activities and modification to the current Office of Administrative Management to accommodate FTE as well as significant command and control reductions. Finally, NHLBI's streamlining effort allowed us to reach our FY 1994 and FY 1995 targets, and our allocations for GS-14 and above positions.

The Institute has also implemented a career track initiative described in the justification. Institute guidelines have been developed and distributed that create three career tracks for mid-level employees. These career tracks were designed to provide for career development of staff, particularly women and minorities. Additionally, the development of these new mid-level positions allowed for a redistribution of work conducted by our senior level extramural program staff to lower graded staff, thus allowing senior research administrators greater freedom to concentrate on science versus administration. These positions are actively being used on our extramural programs.

Finally, the Institute started a Human Resource Management (HRM) initiative, which provides a framework and guiding principles by which to look at HRM activities within the Institute, is active and ongoing. Four working groups, made up of Institute staff representing all grade and job series, have been established as follows: 1) recruitment; 2) selection; 3) retention; and 4) training/career development. The groups are developing recommendations to improve activities within these areas based on employee input and concerns. It is expected that initial group reports will be completed by June, 1995.

Mr. Porter: Is your approach to reorganizing your Institute one that other Institutes have expressed interest in for themselves?

Dr. Lenfant: NHLBI's plan for streamlining was submitted to the Director, NIH and was further distributed to all other ICDs. Subsequent to distribution, NHLBI was asked to present our streamlining plan at the NIH Director's Leadership Retreat which was held in August, 1994. Additionally a number of other Institutes have met with NHLBI staff to discuss the revised structure and the process used to implement these significant changes.

BONE MARROW TRANSPLANTATION

Mr. Porter: Now that the national bone marrow registry has been transferred from your Institute to the Health Resources and Services Administration, can you offer any advice on how you think it can more efficiently and economically be run?

Dr. Lenfant: Despite very rapid growth in both potential marrow donors and in the number of transplants, the National Marrow Donor Program (NMDP) in the past several years has moved toward greater efficiency and improved performance at all levels. The largest single expense category is recruiting new donors primarily because of the cost of HLA typing. Although it is more costly initially to do complete HLA typing (HLA-A, -B, and -DR) at the time donors are recruited, complete typing of donors is more cost-effective in the long run. Complete typing permits more rapid completion of donor searches for patients with rapidly progressive disease who may not live long enough for the more usual search to proceed. The NMDP should be encouraged to continue to HLA-DR typing more of the donors in the file.

There are more than 100 marrow donor centers participating in the program and, as with any large and growing organization, some are more efficient and cost-effective than others. The NMDP should be encouraged to continue and enhance their quality assurance program for participating centers and their own coordinating center. These efforts may result in eliminating the least efficient marrow donor centers and providing for more effective management of their donors.

The NMDP has a number of committees and subcommittees that provide advice about many aspects of the program. When the organization was started and its policies and procedures developed, the work and advice of these committees was invaluable. Now that the NMDP is maturing and functioning well, it is probably time to review again the charges to each of the committees. At least some of those with overlapping functions could be merged and some with functions now performed effectively by staff might be abolished.

RESEARCH AREAS

Mr. Porter: Identify FY 1994-1996 spending on asthma, sickle cell disease, cystic fibrosis, Cooley's anemia, transfusion medicine, tuberculosis, hemophilia, hypertension, sleep disorders, and cardiovascular disease.

Dr. Lenfant: NHLBI funding for these research areas is shown on the following table:

	1994 Actual	1995 Estimate	1996 Estimate
Asthma	$49,048,000	$50,450,000	$51,950,000
Sickle Cell Disease	47,099,000	48,450,000	49,875,000
Cystic Fibrosis	17,140,000	18,125,000	18,700,000
Cooley's Anemia	14,035,000	14,400,000	14,850,000
Transfusion Medicine	40,381,000	41,500,000	42,800,000
Tuberculosis	5,328,000	5,480,000	5,640,000
Hemophilia	14,984,000	15,400,000	15,900,000
Hypertension	126,323,000	129,900,000	133,700,000
Sleep Disorders	13,230,000	15,500,000	17,800,000
Cardiovascular Disease	725,312,000	746,888,000	767,826,000

Mr. Porter: Explain what would constitute a comprehensive center for heart, lung, and blood diseases, how much such a center would cost to operate, and where it ranks in priority relative to your other initiatives in 1996.

Dr. Lenfant: A comprehensive center for heart, lung, and blood diseases encompasses basic and clinical research projects and core functions conducted in a multidisciplinary environment where exchange of scientific ideas, methodologies, and approaches is facilitated.

However, within current fiscal constraints, such a center is not the most cost-effective way to achieve our goals. It is an expensive instrument and potential benefits must be evaluated against not only the high costs of establishing such a center, but also loss of benefits from research derived from alternative, more focused, research investments as well as imbalance in our research portfolio. For these reasons, currently, establishment of a comprehensive center is a relatively low priority for the Institute. The cost of operating each comprehensive center is estimated to be $3,000,000 each year. The Institute feels that a program of this type requires a commitment of ten years in order to adequately evaluate the concept. We believe that the broad goal of a comprehensive center can be addressed by investigator-initiated research that constitutes our portfolio of regular research grants. Mechanisms, other than that of a center, allow the "center concept" to be implemented in institutions by encouraging close interactions, scientific collaborations, and communications among regular research grant investigators. A good example of such a mechanism is the Institute's programs of Collaborative Projects in Women's and in Minority Health. Their special feature is collaboration of regular research grant investigators on a common scientific theme that does not require extensive shared physical resources or core functions to conduct the research.

In the event the Institute should choose to begin a comprehensive heart, lung, and blood research center, it is anticipated that intense competition would mean only the very best peer reviewed research would garner approval for funding. The Institute would do its best to ensure such an outcome.

LYMPHANGIOLEIOMYOMATOSIS (LAM)

Mr. Porter: I understand that NHLBI may be the relevant Institute for research on the disease known as lymphangioleiomyomatosis (LAM). Can you describe this disease, how many people may be affected by it, and how much funding is targeted to its study.

Dr. Lenfant: Lymphangioleiomyomatosis (LAM) is a rare lung disease that affects almost exclusively young women of child bearing age and, therefore, is thought to be a hormone-dependent disease. It is characterized by an overgrowth of muscle throughout the lung, causing a blockage of airways, lymphatics and venules. These events result in an accumulation of fluid between the lung and the chest wall and cyst-like formations in the lung tissue, leading to rupture and subsequent collapse of the lungs. Survival time following onset of symptoms can range from a couple of years to more than 30 years; in one study of 32 patients, 78 percent were alive 8.5 years after the onset of symptoms. Although we do not have good statistics on the incidence, it has been suggested there are probably a few hundred cases in the United States. Currently there are no funds targeted to study LAM; however, we are actively exploring various research directions with both extramural and intramural scientists. In 1992, the Institute sponsored a workshop on respiratory diseases in women that was attended by many pulmonary experts. LAM was one of the diseases discussed at that time. Should the research community submit high quality research applications, the Institute would make a special effort to fund them.

Mr. Porter: How well established is the scientific base to increase research in this field?

Dr. Lenfant: The scientific base currently available is from studies published in the scientific literature. The largest series reported in the United States is from 32 patients collected over a period of approximately 14 years at two major medical centers. The Institute is exploring with the Office of Rare Diseases the possibility of developing a patient database. We are also encouraging the patients to develop a support group as this can be a very effective way to identify patients. This course of action has been done successfully for two other rare lung diseases, primary pulmonary hypertension and alpha$_1$-antitrypsin deficiency.

TRANSFUSION MEDICINE - BLOOD BANKING

Mr. Dickey: What recent actions have the NHLBI taken to increase the safety of this nation's blood supply?

Dr. Lenfant: The National Heart, Lung and Blood Institute (NHLBI) has taken a very progressive and positive role in assuring a safe blood supply. In FY 1994, the NHLBI funded five research grants to study the inactivation, destruction or removal of infectious agents in cellular components of donated blood, seven research projects to examine why hemoglobin-based blood substitutes are toxic, and one project to evaluate potential human errors in blood banking practice. Seven years ago, NHLBI-supported research resulted in the development and implementation of the most widely used method of inactivating viruses in plasma and plasma protein concentrates (e.g., antihemophilic factor). Until recently, it was assumed that a technique that would inactivate infectious agents would also severely damage blood cells. However, new approaches seem promising for overcoming this disadvantage. Inactivation procedures have the potential of protecting against new and unknown infectious agents, as well as against those currently known (e.g., HIV, Hepatitis B and C).

Hemoglobin-based blood substitutes would be an invaluable infection-free material that could replace red blood cell transfusions in many disease and injury states that require transfusions. Currently, these compounds have serious toxic side effects. The NHLBI-supported research is designed to determine why these preparations are toxic and how this problem can be eliminated. Another NHLBI-supported project is investigating human error in the blood bank setting with the objective of modifying systems, if necessary.

The NHLBI continues to support research projects of great importance to the goal of improving blood transfusion safety. One of the most important involves the refinement of gene-based tests for HIV and other viruses potentially transmissible by transfusion. One method can be at least partially automated and used for mass screening of blood donors; another method uses a self-contained pouch and can easily be done at odd hours in small numbers by qualified, but less experienced personnel. This later approach will fulfill the testing needs for organ donation. These tests detect the virus, rather than an antibody to the virus that takes time to develop after the infection starts ("window" period). Gene-based tests considerably shorten this "window" period.

Another continuing project, the Retrovirus Epidemiology in Donors Study (REDS), has collected valuable information about risky behavior for infection by HIV or other viruses in blood donors. This information will foster improvements in blood donor screening practices that will improve transfusion safety. Finally, the Transfusion Safety Study (TSS), initiated in 1984, has provided preliminary evidence that Creuzfeldt-Jakob disease (CJD), a frequently fatal brain disease with severe dementia, is not likely to be transmitted by plasma protein concentrates. Although more research is needed, CJD is less likely to be a serious threat to patients with hemophilia treated with clotting factor concentrates.

NATIONAL CENTER ON SLEEP DISORDERS RESEARCH

Mr. Dickey: What advances have been made by the National Center on Sleep Disorders Research on the problem of sleep apnea (temporary cessation of breathing during sleep)?

Dr. Lenfant: The National Center on Sleep Disorders Research (NCSDR) is making significant progress on the problem of sleep apnea. Results from the first large scale epidemiological study have now clearly demonstrated that sleep apnea and accompanying daytime sleepiness is very common in the general population, with 4% of men and 2% of women meeting the minimum diagnostic criteria for sleep apnea. Both gender and obesity are important risk factors, and severe sleep apnea results in greater daytime sleepiness. Another population based study suggests that sleep apnea has a genetic basis; 46 percent of Caucasian families and 68 percent of African-American families of individual sleep apnea patients also have other family members with sleep apnea. The relationship between sleep apnea and age appears to be different for white and black families. There is a much weaker relationship of increasing apnea with age in black subjects, and a greater proportion of young apneics are black than white. Upper airway anatomic factors appear to play a key role for differences within and between family members.

Another important advance is the mounting evidence that sleep apnea patients may have alterations in cardiovascular control that predispose to adverse cardiovascular events and even sudden death. New findings demonstrate that sleep apnea, ranging from mild to moderate severity, is an independent risk factor for hypertension and elevated blood pressure during both wakefulness and sleep. These results show that the normal decline in blood pressure during sleep is diminished in persons with severe sleep apnea. In fact, blood pressure increases immediately following an apnea, and transient arousals with reductions in oxygen levels enhance the magnitude of the blood pressure response. The NCSDR is following up on these advances by supporting a large multi-center study to determine the cardiovascular consequences of sleep apnea, which should provide new insights on whether sleep apnea is an independent or contributing risk factor for the development of cardiovascular disease and stroke.

Finally, the NCSDR is developing professional education materials for primary care physicians to recognize patients with sleep apnea. Coupled with this effort is a mass media campaign to increase public awareness about the signs and symptoms of sleep apnea, with special emphasis on targeting patients with undiagnosed sleep apnea.

STROKES AND HEART ATTACKS

Mr. Dickey: To what extent does hypertension contribute to incidence of strokes and heart attacks?

Dr. Lenfant: Hypertension, or elevated blood pressure, is the most important modifiable risk factor for the development of stroke. Data from NHLBI studies at Framingham indicate a steady increase in stroke risk with increasing blood pressure; a person's chance of having a stroke more than doubles when systolic blood pressure increases from 120 mm HG to 180 mm HG. Only 20 percent of all strokes occur in persons who have no hypertension.

Hypertension is a strong risk factor for the development of coronary heart disease (CHD). An increase in systolic blood pressure from 120 to 180 also doubles the chance of developing CHD. Only 25 percent of all CHD cases occur in persons who have no hypertension. Other risk factors for CHD include elevated cholesterol, cigarette smoking, diabetes and overweight. In the U.S. 27.1 percent of the population have hypertension, 22.4 percent have elevated cholesterol, 30.3 percent are current cigarette smokers, 3 percent have diabetes and 35.2 percent are overweight.

Mr. Dickey: Given a person's smoking habits, nutritional intake, frequency of exercise, and disposition to hypertension, to what extent can a person prevent a stroke or heart attack?

Dr. Lenfant: Studies show that, on average, each of the following risk factors -- smoking, high blood cholesterol, high blood pressure, and physical inactivity -- approximately doubles the risk of coronary heart disease (CHD), which causes heart attacks. If a person has an average level of any one of the risk factors, they could approximately cut their risk of heart attack in half by eliminating that risk factor. The higher the level of the risk factor (for example the higher a person's blood pressure), the greater the risk, so that any degree of reduction in the factor will help reduce risk. Diet can decrease excess weight, reduce blood cholesterol and reduce blood pressure. Data from the Multiple Risk Factor Intervention Trial (MRFIT) indicate that men who had all three risk factors at the highest level, in other words, men who smoked and also were in the highest 20% for both blood cholesterol and blood pressure, had 20 times the risk of CHD death as the men who had none of the factors. Although the absolute magnitude of risk in women is lower than that in men, the relative contributions of the risk factors are similar. The same risk factors affect stroke, but the effect of cholesterol is lower and the effect of high blood pressure is greater than for CHD.

EDUCATION PROGRAMS

Mr. Dickey: What percentage of your resources are used to educate people on the behaviors found to avoid cardiovascular problems?

Dr. Lenfant: The FY 1994 actual for NHLBI education programs was $11,117,000, approximately one percent of the total budget. In addition to these programs, the Institute also provided $84,854,000, or 7 percent of the budget for research on health and behavior.

Mr. Dickey: Recent reports have raised questions about the effectiveness of cardiopulmonary resuscitation (CPR). According to your data, what is the effectiveness of CPR?

Dr. Lenfant: For many years, periodic reports have questioned the effectiveness of basic CPR, especially as performed by citizen bystanders on victims of cardiac arrest outside the hospital setting. The fact remains however, that prior to the advent of CPR, the survival rate from cardiac arrest was extremely low. Although CPR alone will generally not succeed unless it is followed by the timely administration of more advanced resuscitation techniques, such as electric defibrillation, it has been shown to improve the likelihood of survival in many studies, especially where advanced emergency medical services take several minutes to arrive on the scene. Simply stated, CPR buys valuable time until definitive therapy can be given.

Over the nearly 35 years since the advent of CPR, a number of studies, have helped to identify the factors associated with successful resuscitation, and ways to improve survival rates from cardiac arrest. Much research remains to be done in the area of public education about cardiac arrest, especially the vital importance of prompt CPR and notification of emergency medical services. The NHLBI's National Heart Attack Alert Program is actively engaged in increasing public awareness about heart attack and cardiac arrest. Benefits of such education include increased awareness of factors leading to or preventing heart disease, recognition of a cardiac arrest, increased use of effective bystander-initiated CPR and improved activation of the local emergency medical system.

ADVANCES IN TREATMENT AND CURE OF ACUTE ASTHMA

Mr. Dickey: What recent advances have been made in the treatment and cure of acute asthma?

Dr. Lenfant: Research has not yet found a cure for acute episodes of asthma. However, many acute episodes can be prevented. Recent advances in our understanding of asthma emphasize that asthma is not just a disease with isolated episodes that come and go. Rather, it is a chronic disorder of inflammation in the airways that makes the airways sensitive and causes acute episodes. When the inflammation is controlled with appropriate therapy, then episodes can be prevented.

The NHLBI supports several educational and research efforts to advance treatment of asthma. The NHLBI's National Asthma Education and Prevention Program Expert Panel Report: "Guidelines for the Diagnosis and Management of Asthma" provides a structured approach to asthma management that is based on recent findings from scientific studies. Major ongoing studies include the Childhood Asthma Management Program, which compares the long term effects of three different medications in children age 5-12 years; the Asthma Clinical Research Network, which has two projects comparing different therapeutic approaches in adults; and in partnership with the National Institute of Child Health and Human Development, a study of medications for pregnant women with asthma.

SICKLE CELL DISEASE

Mr. Stokes: As you know, every year I ask you about progress in sickle cell disease. So, I am sure you can imagine -- I was encouraged by the recent research finding of the drug that reduces the pain crisis associated with sickle cell disease. Would you update the committee on the sickle cell finding and related progress in the treatment and diagnosis of this disease?

Dr. Lenfant: On January 30, 1995, the National Heart, Lung and Blood Institute announced the results of a clinical trial of hydroxyurea in decreasing sickle cell related painful episodes by 50% in severely affected adult patients with sickle cell disease. In addition, hydroxyurea also reduced the rate of acute chest syndrome, a pneumonia-like illness by approximately 50%; and the patients treated with hydroxyurea in this study required fewer transfusions during this period. These findings were so dramatic that a Data and Safety Monitoring Board (DSMB), which advises the Institute on the conduct of this clinical trial, recommended that the study be terminated four months earlier than planned. A Clinical Alert announcing these findings was released to the practicing physicians and patients in the study were notified of these results.

Mr. Stokes: What hope does this finding offer children suffering from this disease?

Dr. Lenfant: This therapeutic approach is equally as promising for pediatric patients, however, it is premature to fully extrapolate these findings from the adult study to children. Presumably, the mechanism of action of hydroxyurea would be the same leading to some therapeutic benefit. We anticipate that clinicians will want to consider hydroxyurea in children and have initiated a small safety and dosing study of hydroxyurea in severely affected children through four of our Comprehensive Sickle Cell centers. Because the long term untoward effects of hydroxyurea are not known, we are recommending that caution be the guide for using this drug in growing and developing children.

Mr. Stokes: As disease prevention, early detection, and treatment, collaboration between the Centers for Disease Control, the National Institutes of Health, and the Food and Drug Administration have proven to result in the accelerated application of advances stemming from biomedical research. To what extent will a similar collaborative approach be used to advance the recent development of the sickle cell therapy -- in an effort to improve the quality of life for those suffering from this disease?

Dr. Lenfant: The recent advances of hydroxyurea therapy are extremely promising for selected adult patients with sickle cell anemia. The opportunity to maximize this therapeutic approach will require close collaboration with the Food and Drug Administration (FDA) for a number of reasons. First of all, hydroxyurea is not approved for use in sickle cell disease, and it will be critical for the FDA to work with the manufacturer to evaluate the data from the Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia for "on-label" use. In addition, there is increasing interest in using this drug in pediatric patients. The Institute recently began a pediatric study of hydroxyurea at four of the Comprehensive Sickle Cell Centers. Collaboration with the FDA to evaluate this pediatric data is essential to the expanded use of hydroxyurea in children. The Centers for Disease Control (CDC) could be invaluable in disseminating the results of this clinical trial through their programs on minority health.

Mr. Stokes: What additional research is underway to further advances in the treatment of sickle cell disease?

Dr. Lenfant: Although the recent therapeutic advance is a giant step forward, the Institute continues to pursue parallel efforts in other areas of research directed at improving the treatment of patients with sickle cell disease. We recognize that hydroxyurea is not the drug of choice for all patients and the NHLBI supports research on other agents that increase fetal hemoglobin. One such group of non-cytotoxic agents, butyrate salts, are under investigation. The hematopoietic growth factor, erythropoietin, also increases fetal hemoglobin and preliminary studies of hydroxyurea and erythropoietin indicate that there is a synergistic effect with these two agents. Other approaches examine mechanisms that effect water and ion transport. A small number of selected patients have been treated successfully with allogeneic bone marrow transplantation and ongoing research is designed to further decrease the risks of this therapeutic option.

Mr. Stokes: What opportunities in sickle cell disease are ready to be exploited?

Dr. Lenfant: Recent advances in genetics, cell and molecular biology have greatly expanded the research opportunities in sickle cell disease research. Several areas identified by a Sickle Cell Task Force, convened by the NHLBI, are receiving extensive investigation. These include studies of the endothelium, the microvascular environment, the coagulation system and their respective contributions to the pathophysiology of sickle cell disease. In response to the Institute's announcement to encourage research on gene therapy for sickle cell disease, we recently funded three program projects with the ultimate goal of curing this disorder. Our basic research emphasis in stem cell biology has significant application to sickle cell disease.

Mr. Stokes: How much is included in the FY 1996 budget request for research on this disease, and how does it compare to FY 1995 and FY 1994?

Dr. Lenfant: The FY 1996 budget includes $49,875,000 for sickle cell disease research. This compares to an FY 1995 estimate of $48,450,000 and a FY 1994 actual obligation of $47,099,000.

CALCIUM CHANNEL BLOCKERS

Mr. Stokes: What can you tell us about the increasing precautionary measures and concerns surrounding the use of calcium channel blockers in the treatment of heart disease-- how serious is this problem?

Dr. Lenfant: Calcium channel blockers are a class of drugs widely used for treating high blood pressure and heart disease, particularly angina pectoris. About five years ago several reviews of clinical trials studying the use of calcium channel blockers in patients with diagnosed heart disease suggested that these drugs did not appear to prevent heart attacks, strokes, and other cardiovascular complications, and certain sub-types might even increase the risk of these occurrences. The evidence was statistically weak, however, and calcium channel blockers continued to be recommended and used as one of several options for the conditions in question.

A new study supported by the Institute was reported for the first time at an American Heart Association conference on March 10. The study found an approximately 60 percent higher rate of heart attacks in patients taking a calcium channel blocker for high blood pressure compared to those receiving a diuretic or a beta-blocker. However, in this "case-control" study the choice of which drug to prescribe was not under the control of the researcher but was decided by the individual's physician for reasons not always clear in the medical record. Whether the specific treatment under study or whether some other aspect of the patient's condition or treatment is responsible for various outcomes is difficult to determine.

The NHLBI is currently sponsoring the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a 9-year study that will eventually involve 40,000 patients (half of them African Americans) in order to determine which of several drug classes--including calcium channel blockers--are best for reducing the risk of heart attacks in older persons with hypertension. These and other NHLBI trials that include calcium channel blockers have Data and Safety Monitoring Boards that monitor the study at regular intervals for life threatening complications related to the study drugs and would promptly determine if any additional precautions are necessary for participating patients. I should point out that the ALLHAT project is complex and fraught with difficulties, particularly our abilities to recruit new patients. We hope that this problem will not force us to end the project. Meanwhile, in order to reassure patients in the wider community, the NHLBI has issued a statement that changes in treatment guidelines are not warranted based on a single case-control study, especially since the study has not yet been published.

BONE MARROW

Mr. Stokes: According to your Congressional justification, we are beginning to see advances in the area of bone marrow transplantation. It appears that researchers have discovered that blood obtained from the placenta after birth has been shown to be an effective alternative to bone marrow transplantation. Doctor, would you elaborate on the significance of this finding.

Dr. Lenfant: Many investigators believe that cord blood or placenta blood transplants may not require as careful tissue-type matching as bone marrow. Even with incomplete matching, there may be less frequent and less severe graft-vs-host disease. The National Marrow Donor Program (NMDP) has made great strides in recruiting marrow donors from minority groups. Nevertheless, it is considered by some investigators to be easier to collect cord blood units from minority-group placentas than to recruit adult marrow donors. As a supplement to the NMDP donors, cord and placenta blood banks could improve the chances of a minority-group patient finding a match for a needed transplant. The most important and exciting advantage of such transplants will occur if one or two antigen mismatches can be transplanted with acceptably low graft-vs-host disease. If possible, unrelated-donor cord and placenta blood transplants can be extended to patients with sickle cell anemia, severe Cooley's anemia and other highly symptomatic, but not rapidly fatal disorders. Much research will be needed to determine if these noted advantages are valid, if cord and placenta blood transplants can be successful in large children and adults, and if potential risks of transmitting infectious diseases (e.g., HIV infection) can be eliminated. The National Heart, Lung, and Blood Institute is planning to provide increased resources to obtain answers to these and other questions concerning cord and placenta blood stem cell transplantation.

ASTHMA

Mr. Stokes: As you know, far too often, because of the degree of asthmatic attacks, patients suffering with asthma are forced to resort to emergency facilities for care during such attacks. Over the years, a lot of attention has been given to self-management of the disease. What major research is underway in this area?

Dr. Lenfant: The Institute supports demonstration and education research projects on asthma to identify effective approaches for improving asthma management in a variety of clinical and public health settings. Several self-management programs targeting children and adults have been developed, tested, and disseminated nationally. Study results indicate that the programs led to improved overall management of asthma, reduced emergency department visits and hospitalizations, and reduced school days lost. The asthma education programs have been adopted by clinic programs, large scale health maintenance organizations, and health insurance providers and public organizations seeking to promote effective asthma management.

The Institute currently has five research projects that are developing and testing innovative educational strategies to manage asthma in black and Hispanic children, who suffer disproportionately from asthma morbidity and mortality. Study findings and a document highlighting the lessons learned from the five projects are now being prepared. The next steps are to identify key elements from the projects to develop and evaluate model asthma education programs for widespread dissemination among minority populations.

Mr. Stokes: Are we making significant inroads in unraveling the cause of this disease, improving the treatment, and ultimately preventing asthma?

Dr. Lenfant: Dramatic advances in genetic studies of complex human diseases now provide a new approach to studying asthma. Through programs sponsored by the NHLBI, the application of molecular genetic approaches and cell culture methods is leading to insights into the genetic factors causing asthma. The search for genetic factors has taken a promising turn with findings indicating that several genes may be important in the regulation of allergic responses and the pathogenesis of asthma.

Another exciting new finding offers hope that children at high risk for developing asthma can be identified early and treated before the disease has begun to impair lung function, thereby stemming the course of the disease. Epidemiologic studies now indicate the existence of two different wheezing syndromes in children during the first three years of life, exhibiting completely different risk factors, and one of which predisposes to early onset asthma. One, called "early wheezers," is mainly associated with congenitally diminished lung function, but lacks airways responsiveness and other risk factors associated with asthma. Two-thirds of the children who wheeze as infants fall into this group and will stop wheezing by the age of 6. The other syndrome, called "persistent wheezers" and equated with early onset asthma, is associated with risk factors for asthma, such as increased prevalence of allergic markers, airways hyperresponsiveness, maternal history of asthma, maternal smoking, and a significant deterioration of lung function during the first six years of life despite normal levels during the first year of life. These new findings help to increase our understanding of asthma so that we may improve not only the management and treatment of this disease, but also represent an important step forward in its prevention.

The NHLBI has several research programs to improve treatment, including clinical trials that investigate new therapies and evaluate the long term effectiveness and safety of different medications for control of asthma. For example, the Childhood Asthma Management Program compares the long term effects of three different medications in children age 5-12 years; the Asthma Clinical Research Network has two projects comparing different therapeutic approaches in adults; and in partnership with the National Institute of Child Health and Development, the NHLBI has a study of medications for pregnant women with asthma. In addition, the NHLBI is convening a special emphasis panel to discuss a comprehensive range of topics in asthma prevention: genetics, epidemiology, characterization of risk factors for the onset of asthma, identification of at risk individuals, interventions to reduce risk, and education. The panel will help identify the most promising concepts in asthma prevention research.

Mr. Stokes: Would you tell us about the National Asthma Education and Prevention Program?

Dr. Lenfant: The National Asthma Education and Prevention Program (NAEPP) was launched in 1989 by the NHLBI and consists of a collective partnership of 35 national, medical, professional, and community organizations as well as Federal government agencies. The NAEPP is committed to improving the prevention, management and control asthma. It is a major vehicle to effect research translation and information dissemination to critical consumer audiences. The NAEPP's strong outreach efforts in professional education patient/public education and school asthma education has resulted in a coalition of partners to get desired asthma education messages and materials directly to consumers. For example the NAEPP adapted the "Guidelines for the Diagnosis and Management of Asthma" into a kit targeted specifically to emergency department physicians and nurses and has launched a public media campaign to help patients and clinicians take asthma seriously and help patients get regular care. Additionally, a kit was published to help clinicians teach patients about asthma management and be effective partners in their asthma care.

Mr. Stokes: To what extent has research conducted by the Institute resulted in reducing the number of hospital visits for asthma, and what is the associated health care cost savings?

Dr. Lenfant: Studies of asthma education programs and cost of illness studies supported by NHLBI have demonstrated that preventive treatment and education interventions lead to reduced emergency department visits, hospitalizations, school days lost. This leads to cost savings for the patient, family, and health care system. Studies have indicated, for example, that the cost of preventive treatment may be a fraction of the cost of the averted hospitalization. One study, for example, showed that an education program that cost $82 per patient resulted in $628 per patient savings in emergency room costs. The Institute convened a Task Force on Cost-Effectiveness, Quality, and Financing of Asthma Care to review studies that assessed the economic burden of asthma and the economic impact of effective asthma care programs. The task force report will provide the NHLBI with data on costs, and will make recommendations for future research and translation activities that will promote cost-effective asthma care.

Mr. Stokes: What opportunities in asthma research are ready to be exploited?

Dr. Lenfant: Asthma results from the combined effects of genetic and environmental factors, but the nature of the gene or genes that contribute to this predisposition remains to be established. Understanding the genetic and environmental causes of asthma is essential to the primary prevention of this disease and to its improved diagnosis and treatment. The application of new genetic approaches to the study of asthma could lead to the identification of the major genes responsible for asthma. Gene functions can be identified by observing the results of inactivation (knockout mouse) or overexpression (transgenic mouse) of a targeted gene. Transgenic animal models of asthma affords a powerful means to better define the pathogenesis of the disease and to test specific hypotheses related to asthma. In the past 5 years, a number of special proteins (cytokines, adhesion molecules, receptors, and growth factors) have been identified as pivotal elements in asthma. "Designer" animals can now be developed to explore the role of these special proteins in the pathogenesis of asthma.

Inflammation is recognized to be one of the most important components in the pathogenesis of asthma. Using the tools of molecular biology, the inflammatory and immune processes, including the role of specific cells and cells products that regulate these precesses can now be better defined. The availability of these technologies and their expanded applications to studies of asthma should lead to accelerated progress and new therapies.

Mr. Stokes: How much is included in the FY 1996 budget request for research on this disease, and how does it compare to FY 1995 and FY 1994?

Dr. Lenfant: At the FY 1996 request level, the NHLBI estimate for asthma research is $51,950,000. This compares to a FY 1995 estimate of $50,450,000 and a FY 1994 actual of $49,048,000.

CORONARY HEART DISEASE

Mr. Stokes: What is the extent of coronary heart disease in the United States?

Dr. Lenfant: It is estimated that nearly 13 million persons in the United States have coronary heart disease (CHD); this number includes 6.5 million with myocardial infarction (heart attack) and 6.30 million with angina pectoris (chest pain). These estimates are derived from standard health interview questions from a national survey conducted in 1988-1991. Total prevalence amounts to 7.2 percent of the adult population.

Mr. Stokes: Which segments of the population are most adversely impacted by this disease?

Dr. Lenfant: The percent of persons with CHD rises with age. Out of the 223 million people under age 65, 7.7 million persons have CHD; out of the 32 million people age 65 and over, 4.9 million have it. The percent of persons with CHD is appreciably higher in men than women in each age group. Unlike mortality from CHD, which is higher in the black than the white population, prevalence is about the same in black and white men and is only slightly higher in black than white women. Prevalence is lower in Hispanics than in the white and black populations. There is higher prevalence of CHD in persons of lower compared to higher socioeconomic status. Since estimates are based on self reporting, reporting bias may affect the accuracy of these demographic comparisons.

Because black Americans experience a disproportionate number of deaths from coronary heart disease, the NHLBI has initiated efforts to develop intervention strategies to address this burden in the African American population. The Institute has begun to work with Historically Black Colleges and Universities, particularly those with medical schools, and with African American professional organizations such as the Association of Black Cardiologists, National Medical Association, Student National Medical Association, and National Black Nurses' Association, to conduct a variety of outreach and education activities to promote healthy lifestyle behaviors and thereby reduce or prevent CHD risk factors in African Americans. A significant effort will be a major Forum on the Status of CHD in the Black Population cosponsored by Howard University and held on March 31, 1995 with a focus on preventing, managing, and controlling hypertension in the African American community.

Mr. Stokes: To what extent are there efforts underway to address coronary heart disease in at-risk populations?

Dr. Lenfant: A number of clinical trials and demonstration studies are targeted to populations at higher risk due to race/ethnicity, age, educational level, and socioeconomic status. These efforts address stages in the development and course of coronary heart disease ranging from preventing obesity in children to promoting a rapid response to acute coronary symptoms in adults. For example, one study (PATHWAYS) is preparing to test an elementary-school-based obesity prevention program in cooperation with four Native American tribes. Another long-standing study of several thousand black and white girls (the NHLBI Growth and Health Study) is developing an understanding of the factors that lead to much higher rates of obesity in African American women, and should provide the basis for subsequent prevention efforts. Four years ago, five groups of researchers were funded to develop and test CHD prevention nutritional education programs for adults of diverse ethnic backgrounds and with limited literacy skills; these projects are nearing completion. The largest clinical trial yet undertaken by the NHLBI, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial, is aiming to enroll 55% African Americans among its 40,000 subjects with high blood pressure, in order to identify the optimal medication(s) for reducing heart attack rates. Finally, in order to test methods to reduce time-to-treatment delay in heart attack patients a community education trial (Rapid Early Action for Coronary Treatment) will soon be underway in 20 communities around the country, including eight communities with large percentages of African Americans and Hispanics.

Mr. Stokes: Doctor, I was pleased to learn that the Institute convened a working group on Research on Coronary Heart Disease (CHD) in Blacks, and that the Institute plans to advance research knowledge in this area through exploitation of research in molecular biology, physiology and clinical practice. Why are these particular areas of research most important?

Dr. Lenfant: In order to address disparities with respect to prevention, diagnosis, treatment and outcomes of CHD in blacks, the working group assessed the state of the science and identified research opportunities in several areas including mechanisms of disease; clinical presentation, diagnosis and treatment; risk factors; behavior; and strategies for education and prevention. The working group identified ten priority research areas, which, in addition to the areas you mentioned, include epidemiology, prevention, risk factors, vascular biology, left ventricular hypertrophy, coronary microvasculature and sudden cardiac death. Although most studies show that there is little difference in the nature of the atherosclerotic process (the underlying disease) leading to CHD in blacks, there are important differences in the prevalence of conventional risk factors, physiologic parameters and the social and economic context in which CHD develops in blacks. For example, blacks have a higher prevalence of left ventricular hypertrophy, hypertension, diabetes, and obesity compared to whites. Elucidation of how these risks result in CHD morbidity/mortality not only will be of particular benefit to blacks but represents a new focus for CHD research. The Institute recently launched a new centers program to investigate coronary heart disease in blacks with a focus in one of three topic areas: diabetic heart disease, microvascular disease; and sudden cardiac death.

Mr. Stokes: How long would it be before we have some significant answers to this major health problem?

Dr. Lenfant: Research on CHD has resulted in a steady decline in death rates due to heart disease for all populations since the 1960's. Although not as rapidly among the African-American populations. Through investigations focused on high risk populations, such as blacks, it is hoped that the rate of decline for minorities will parallel that observed in the majority population. In addition to basic science and clinical investigations, the Institute supports a number of activities in its National Education Programs which give special attention to high risk patients and minority populations in particular. Recommendations and guidelines specific for blacks are often identified. The Institute is fully committed to eliminating racial disparities in cardiovascular health and hopes that the fruits of this commitment are near.

HYPERTENSION

Mr. Stokes: Do we know anymore about the role that genetics plays in hypertension than we did last year?

Dr. Lenfant: Within the past five years, a number of hypertension researchers have adopted molecular genetic techniques to identify causative genes for high blood pressure and to clarify the mechanisms by which these genetic defects lead to hypertension. In addition, some prominent geneticists have also turned their attention to the study of the disease, and as a consequence, our knowledge about the genetic underpinnings of high blood pressure is beginning to accelerate.

The past year has led to the discovery of two new genes involved in salt-sensitive hypertension. Recent studies using the most common animal model for genetic hypertension -- known as the spontaneously hypertensive rat -- have led to the identification of a gene that codes for kallistatin, a substance which inhibits an important regulatory system for blood pressure control. Scientists are now attempting to determine if this same substance is also linked to salt-sensitive high blood pressure in humans. In addition, a second gene involving salt sensitivity was recently linked to high blood pressure. This gene codes for a kidney protein that allows the body to reabsorb sodium. In a condition known as Liddle's syndrome, this protein appears to be overactive, leading to excess absorption of sodium and high blood pressure. What is particularly exciting is that a similar genetic defect may also be present in humans with salt-sensitive hypertension, a very common form of the disease that is particularly prevalent in African Americans.

It is important to understand the genetic abnormalities that result in high blood pressure so that clinicians can identify more discrete diagnostic subgroups, thus allowing for more effective treatment and for the development of better preventive strategies. We hope that the inception of two new research programs, the Genetic Determinants of High Blood Pressure and the Specialized Centers of Research on the Molecular Genetics of Hypertension, and two new scientific resources, the Mammalian Genotyping Service and the Rat Genome Project, will escalate the pace of discovery in this area.

Mr. Stokes: Are we seeing an increase or a decline in this disease?

Dr. Lenfant: High blood pressure continues to be a common finding in the general population. The most recent population data obtained from the Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1991, indicates that 24 percent of Americans have hypertension. The overall prevalence is slightly higher among men than women, and blacks have higher prevalence rates (approximately 28 percent) than whites (approximately 25 percent) or Hispanics (approximately 14 percent).

The NHANES III is our best source of data for estimating the prevalence of essential hypertension in the general U.S. population. Compared to similar data in NHANES II (1976-1980), the overall prevalence of high blood pressure in the general adult U.S. population has decreased from 29.8 percent (almost 60 million individuals) to 24 percent (50 million individuals). As in NHANES II, blacks continue to have a higher burden of the disease, although the overall prevalence for this racial group has decreased from 38.2 percent to 28 percent. In addition, the percent of all hypertensives who are being treated for the disease and who have controlled their condition has increased from 11 to 24 percent.

Prevalence of high blood pressure seems to be on the decrease. Furthermore, awareness, treatment, and control of hypertension have improved substantially since the 1976-1980 survey, and we hope to achieve even better results over the next five to ten years. Improvement can be achieved through a more widespread use of lifestyle modification, as well as through more effective application of available pharmacologic therapy. Treatment may also become more effective with stratification of the general population into more discrete diagnostic subgroups, based not only on race and gender, but on genetic typing, a procedure that may begin to become available within the next decade.

CHOLESTEROL AND ATHEROSCLEROSIS

Mr. Stokes: Are we getting any better at controlling the cholesterol that is highly implicated in this disease (atherosclerosis)?

Dr. Lenfant: Considerable advances have occurred in our ability to control cholesterol and through this to reduce heart attack rates. The recently introduced statin class of drugs are proving very effective in producing 20-40% reductions in blood cholesterol levels, have very few serious side-effects, are easy to take, and are being more extensively used for treatment.

Clinical trials of statin drugs are showing 30-40% reductions in fatal and non-fatal heart attacks, and in total mortality. Reductions of this magnitude, if widely applied, will have a substantial impact on the national heart attack problem.

Guidelines for management of high blood cholesterol have been updated by the National Cholesterol Education Program and now place particular emphasis on treating high cholesterol patients with a history of coronary heart disease. The potential of reducing recurrent fatal or nonfatal heart disease is very high in this group, and is also likely to be associated with considerable cost-savings due to associated reductions in bypass surgery, angioplasty and other expensive procedures.

Mr. Stokes: What research opportunities are ready to be exploited in this research area?

Dr. Lenfant: A variety of opportunities have emerged as possible approaches to improve our control of atherosclerotic disease. Gene therapy, as a means of reducing high cholesterol levels in people with severe hereditary high cholesterol, is undergoing development and appears promising. Gene therapy approaches that use methods to deliver genes to specific locations within the blood vessel to prevent the growth of smooth muscle cells that lead to blockage of coronary arteries after angioplasty (restenosis) is another area with potential. Now that it is known that oxidation of the cholesterol-rich low density lipoprotein (LDL) helps promote atherosclerosis, clinical trials of agents to prevent oxidation of LDL are an important avenue to pursue. Discovery of the high prevalence of a condition called homocysteinemia in heart attack patients suggests a need to consider clinical trials using agents that reduce the high levels of homocysteine.

TRANSFUSION SAFETY

Mr. Stokes: To what extent have we been able to improve the safety of the nation's blood supply?

Dr. Lenfant: Although it is difficult to precisely determine the frequency of rare events, such as the transmission of viral diseases by blood transfusion, the Institute has data that shows the blood supply is safer than ever. The NHLBI's Retrovirus Epidemiology and Donors Study (REDS) has provided the best and most current figures, which are remarkably similar to figures generated by the Centers for Disease Control and Prevention (CDC) using a different approach. In the past 10 years of testing donated blood for HIV antibodies, the likelihood of transmitting HIV by blood transfusion has decreased more than 8-fold and is now 2.4 per million or (1:417,000). The NHLBI is supporting studies to refine tests that can further decrease this probability.

The frequency of transfusion-associated hepatitis has also been substantially reduced in the past 10 years. Non-A and non-B hepatitis, as designated 10 years ago, have been found to be mostly hepatitis C. With the development and refinement of a specific test for hepatitis C antibodies, its frequency following blood transfusion has decreased to minute levels. The NHLBI provided many of the test samples from repositories collected through the years to validate tests for hepatitis C, as well as for other infectious diseases.

In the past year, the Institute has started two new programs: one to study approaches to inactivating infectious agents, either known or unknown, that might be present in donated blood and the other to determine if the toxic effects of hemoglobin-based blood substitutes are due to impurities or to something inherent in the hemoglobin molecule. Techniques for inactivating infectious agents in plasma and proteins derived from plasma have been available for sometime; however, there was concern that any procedure that would inactivate a virus would also severely damage blood cells. New information suggests that developing an acceptable procedure for inactivating viruses in cellular blood components has improved. The development of safe and effective oxygen-carrying blood substitutes, such as those based on hemoglobin, could replace many of the acute needs for blood transfusion, particularly after trauma.

The Institute will continue its research efforts in this area.

SLEEP DISORDERS RESEARCH

Mr. Stokes: According to the Congressional justification, the National Center on Sleep Disorders offers the Institute tremendous opportunities to focus on the cardiopulmonary aspects of sleep. Wh research questions will this enhanced focus on sleep disorders allo the Institute to address?

Dr. Lenfant: The establishment of the National Center on Sleep Disorders Research (NCSDR) will enable NHLBI to pursue a number of new opportunities related to cardiopulmonary disorders of sleep. One very important basic research question is to understand the fundamental nature of sleep and what the brain is doing during the different stages of sleep. Research is needed to elucidate the neurobiologic mechanisms by which sleep is regulated and controlled, and the genetic expression of various sleep neuromodulators, peptides, and mediators during normal sleep and in sleep apnea. It is now possible to determine what brain cells express sleep promoting genes and whether sleep apnea causes changes in gene transcription and the regulatory signals involved in these genetic events. Also, since sleep apnea has been shown to exhibit familial clustering, further research is needed to determine the hereditary nature of sleep apnea.

Research has shown that sleep apnea can produce excessive daytime sleepiness and diminished cognitive performance. Little is known about the prevalence and magnitude of the neurobehavioral deficits or the role of treatments in reversing them. For example, what are the anatomical, biochemical, physiological, cellular and molecular processes that mediate daytime sleepiness and cognitive deficits? What are the long term consequences of sleep apnea on brain structures and functions? What are the cognitive and social-psychological consequences of sleep apnea, and does the severity of apnea relate to the type of neurobehavioral deficits? Does sleep apnea alter homeostatic or circadian control? Do various treatments for sleep apnea differentially affect neurobehavioral deficits? Further exploration of these interrelated factors, particularly as they are related to morbidity and daytime sleepiness/function, may have important therapeutic implications.

In the clinical area, one important research direction is to understand the role of pharmacological agents compared to behavioral interventions for persistent insomnia. Research is needed to investigate the physiological mechanisms that may account for the potential link between poor sleep, insomnia and cardiovascular disease, and whether insomnia may be predictive for future cardiovascular events. Lastly, it is known that sleep is impaired in the critical care patient. Studies are needed to assess the factors which are responsible for sleep deprivation in the critical care patient, and to develop interventions to minimize sleep disturbance and sleep deprivation in patients recovering from illness or surgery in the critical care setting.

CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and has yielded comparable economic savings. What are some of the most significant clinical trials that are currently underway at your Institute, and what are the expected benefits to be achieved?

Dr. Lenfant: The NHLBI supports a wide range of clinical trials to address important questions related to disease prevention, diagnosis, and treatment. One of them, the Trials of Hypertension Prevention, is being conducted among overweight men and women with borderline high blood pressure, a substantial percentage of whom are minorities, to determine whether a dietary regimen and/or other lifestyle change can prevent definite hypertension. Because hypertension affects approximately 50 million Americans and disproportionately affects minorities, effective non-pharmacological methods of prevention offer great potential for significant improvements in public health and major health care cost savings. Another NHLBI-supported study, the Rapid Early Action for Coronary Treatment trial, is evaluating the impact of community education interventions on patient delay time from onset of a heart attack to seeking care for treatment. It is now well-established that early intervention with thrombolytic agents can reduce mortality and prevent or limit damage to the heart resulting from a heart attack, so this research has important implications for improved public health and reduced health care costs. Approximately 21 percent of the subjects belong to minority groups.

The NHLBI is also supporting major clinical trials in asthma and sickle cell disease, conditions that are of particular concern to minorities. In recent years, asthma incidence, prevalence, and mortality rates have been increasing, with increases among blacks being especially pronounced. In addition, striking differences in asthma mortality exist between black and white children. The NHLBI's Childhood Asthma Management Program is the first trial to compare the effects of anti-inflammatory therapy and bronchodilator therapy on the course of asthma. In accord with the disparate asthma burden borne by minorities, 65 percent of the participants accrued to date belong to minority groups. The NHLBI has also established an Asthma Clinical Research Network, consisting of five clinical centers and a data center, to assess new methods of asthma treatment in clinical trials and to ensure that findings on the optimal management of asthmatic patients are rapidly disseminated to practitioners and health care professionals. Approximately 48 percent of the patients participating in the trials will be members of minority groups. The NHLBI-supported Stroke Prevention in Sickle Cell Anemia (STOP) trial is assessing the efficacy of prophylactic transfusion therapy as a method to reduce episodes of first-time stroke in 120 black children with sickle cell anemia. Stroke is a serious cause of morbidity and mortality for children with sickle cell disease, occurring in 7 to 8 percent of them. Moreover, the rate of stroke recurrence is 45 to 90 percent among children who are not chronically transfused. If shown to be effective, prophylactic transfusion therapy will not only improve the quality of life for sickle cell patients, but also result in substantial savings in avoided medical treatment costs associated with acute stroke hospitalizations.

Mr. Stokes: What level of funding is included in the FY 1996 budget for clinical trials?

Dr. Lenfant: The FY 1996 budget includes $105,000,000 for non-AIDS clinical trials.

Mr. Stokes: How many trials would be funded?

Dr. Lenfant: The NHLBI estimates that approximately 60 to 70 non-AIDS clinical trials would be funded in FY 1996, depending on the number of investigator initiated trials that are funded.

Mr. Stokes: How many of these trials are new and how many are ongoing?

Dr. Lenfant: At the request level, the budget includes funds for 54 ongoing trials. We estimate that we would fund from 6 to 16 new clinical trials depending upon the scientific merit of applications submitted by individual investigators.

CLINICAL TRIALS INFORMATION DISSEMINATION

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously?

Dr. Lenfant: NHLBI uses a variety of mechanisms for relaying the results of clinical trials research to health professionals, patients, and the public in an expeditious manner. We are continuously seeking new means of delivering that information rapidly and effectively. For example, a major means of disseminating such information is through clinical practice guidelines developed by NHLBI's national education programs. We are currently conducting a marketing study to examine the format, organization, and dissemination of clinical information to help us refine the presentation and delivery of our guidelines to physician audiences in the future.

We are also making use of the information superhighway in various ways to deliver our clinical trials results quickly and cheaply. NHLBI's gopher on the Internet makes available the full text of practice guidelines and other clinical information to a broad audience. In addition, the information is made available to a variety of existing bulletin boards, such as Black Bag, that serve clinical audiences. The many health organizations that are partners in NHLBI's education programs are being linked together online to facilitate rapid exchange of information, starting with the 40 organizations that form the National High Blood Pressure Education Program.

When communication of clinical trials results is of the utmost urgency, NHLBI uses the information superhighway and other means to disseminate the information rapidly to the news media and health professionals as a Clinical Alert, using the protocol established by NIH. For example, NHLBI used this methodology in releasing the results of a recent clinical trial on an effective treatment for sickle cell anemia. The clinical information was listed in a special alert section of Medline, a press conference was convened--resulting in very wide news coverage--and treating physicians were alerted, all within 2 weeks of the end of the trial.

Mr. Stokes: Is there a specific system in place for disseminating such information, explain?

Dr. Lenfant: The Office of Prevention, Education, and Control (OPEC) works in two main ways to deliver the results of clinical trials as quickly and thoroughly as possible to health care professionals--through syntheses and with single-trial results. Both ways are handled by the Office's Research Translation and Information Dissemination Program.

Findings from several major trials are periodically synthesized by panels of leading experts into practice guidelines on a particular topic, such as asthma, high blood cholesterol, and high blood pressure. These guidelines are distributed through national education program coordinating committee members, which represent all major professional organizations involved in a particular area, and become standards of practice nationwide.

Single trial results are disseminated rapidly through such means as targeted mailings and satellite teleconferences. For instance, OPEC developed materials to explain results from the NHLBI-funded Studies of Left Ventricular Dysfunction. The materials were mailed to 70,000 physicians through a collaboration with the Alliance for Aging Research. In another case, OPEC is working with the Association of Academic Health Centers to broadcast results from its Postmenopausal Estrogen/Progestin Interventions trial to medical schools nationwide. A similar teleconference will broadcast results from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. These interactive teleconferences give physicians a chance to question the trial scientists personally.

Finally, OPEC works closely with medical writers to assure that important news gets covered immediately via such means as press conferences. It also helps the NHLBI reach health professionals with information for specific audiences, such as women, minorities, and cardiac patients.

AIDS RESEARCH

Mr. Stokes: What is the most significant AIDS research that is underway at your Institution?

Dr. Lenfant: The NHLBI supports AIDS research in the area of blood safety and areas relating to the pulmonary, cardiac, and hematologic complications of HIV infection.

As part of its program on blood safety, the NHLBI continues to support studies to investigate alternative HIV-1 tests that would not depend on the development of antibody to the virus and which would therefore eradicate the possibility of HIV transmission by transfusion. Two different categories of tests are being investigated: those that detect the viral antigen and, more important, those that detect very small quantities of viral DNA or RNA. Progress has been made in developing an accurate method using polymerase chain reaction (PCR) technology and in situ hybridization to detect small amounts of viral DNA and RNA in both blood and tissues. Two NHLBI-supported contractors have developed different techniques that have the possibility of being used in a large-scale fashion for screening blood for transfusion and tissues for transplantation; a patent application is pending.

The NHLBI has been involved in the development of specific immune globulin for prevention of disease. In 1985, the NHLBI supported work by the New York Blood Center to develop an HIV-1 hyper-immune globulin (HIVIG), which was successfully tested in chimpanzees that received HIV-1 virus simultaneously. These investigators demonstrated that HIVIG did prevent infection in chimpanzees. Recently, the NHLBI, along with the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD), began a trial of HIVIG in HIV-1-infected pregnant women. This trial will test the efficacy of HIVIG compared to regular immune globulin (IVIG) in reducing or preventing transmission of HIV-1 to the children who are born. The phase I safety and pharmacokinetics part of the study has been completed and enrollment of patients into the full trial has begun.

HIV-1-related pulmonary disease is responsible for most of the morbidity and mortality associated with HIV infection. Our ability to develop new treatment for Pneumocystis carinii pneumonia rests on our understanding of the basic pathophysiology of the disease. The NHLBI supports a program designed to understand the basic mechanism of attachment of Pneumocystis to pulmonary macrophages. Continued strides in our knowledge of Pneumocystis and its relationship to the lung should improve our ability to develop and screen more drugs with potential activity against the organism. The NHLBI continues its commitment to fostering research in this area. Although tuberculosis (TB) incidence had been steadily decreasing in the years before the advent of the HIV epidemic, recently there has been a dramatic reversal of this trend. Many persons with TB experience significant side effects from anti-TB medications during the lengthy course of drug treatment. This leads to poor compliance and, then, to inadequately treated disease. Substantial benefits would be expected from delivering the drug directly to the lung in aerosol or liposome form. The NHLBI is funding an initiative that will support development of such a drug in fiscal year 1995.

Heart disease is common and progressive in HIV-infected children and adults. It is often clinically inapparent. It appears to be due to both an intrinsic cardiomyopathy (as reflected by reduced contractility of the heart) and to increased afterload. The NHLBI supports a large natural history study of pulmonary and cardiac disease in HIV-infected children. It also supports a study of the role of angiogenesis in Kaposi's sarcoma.

AIDS RESEARCH SPIN-OFFS

Mr. Stokes: To what extent has knowledge gained in AIDS research and breast cancer research had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your Institute?

Dr. Lenfant: The AIDS epidemic imparted a new sense of urgency to NHLBI research efforts to ensure the safety and adequacy of the blood supply. As a result of this research, we now have greater utilization of autologous blood for transfusion, more sensitive procedures to test donated blood for infectious agents, and effective sterilization procedures for coagulation concentrates. AIDS-related studies also provided impetus for development and licensing of an effective blood substitute for use during angioplasty. In addition to reducing the incidence of HIV infection, these advances have reduced transmission of other blood-borne infections, such as hepatitis.

New knowledge gained from breast cancer research can be expected to make a major contribution to our fundamental understanding of the genetics of other complex diseases, such as hypertension, atherosclerosis, asthma, and chronic obstructive pulmonary disease. Science is only at the beginning of its appreciation of the complicated interplay of genetic and environmental influences that contribute to disease development and progression. The technical advances needed to locate a gene responsible for breast cancer in families (BRCA1) will assist efforts to understand the genetics of other diseases by providing improved statistical and analytical approaches, better biological resources (such as high resolution genetic and physical maps), and new methodological strategies for detecting and studying altered genes.

MINORITY HEALTH

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health, in testimony before the committee this year, indicated that the Department is enhancing its efforts to close the health disparity gap. While this issue is complex and a multiplicity of factors contribute to the disparity including lifestyle and access to health care, biomedical research does have a key role to play in helping to close the gap. What can you tell us this year about improvements in minority health as a result of the research conducted by your Institute that you could not tell us when you were here last year?

Dr. Lenfant: Much overall progress has been made during the past year by our minority-related research programs, the most exciting and significant being the recently announced results of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. This trial evaluated use of the drug hydroxyurea, the first therapeutic agent for patients with sickle cell disease to show promise of clinical efficacy without life-threatening toxicity. The trial was halted ahead of schedule when interim analysis of data indicated that daily administration of hydroxyurea reduced the rate of painful episodes ("crises") by more than 50 percent. In addition, hydroxyurea therapy resulted in a significant decrease in acute chest syndrome, a life-threatening complication of SCD. Hydroxyurea therapy also greatly reduced the need for transfusions, a fact that has important public health implications for treatment of patients with SCD.

The Institute has several significant ongoing research activities that address the disparity in minority health. In addition, we believe we can have a positive impact on there differences based on findings from previous research. Therefore, we are making special efforts to work with minority communities to establish a network for a more rapid and effective research translation and dissemination process.

There are several examples. The NHLBI is working collaboratively with the Office of Research on Minority Health, NIH, to promote several goals: increase awareness of the adverse effects of coronary heart disease (CHD) and associated risk factors; increase skills of clinicians to treat and control high blood pressure, high blood cholesterol, and heart attacks; and increase community participation in activities that will promote healthy choices and normal lifestyle behaviors.

These efforts involve working with such organizations as the National Medical Association, Association of Black Cardiologists, the National Black Nurses' Association, Inc., and the Student National Medical Association to conduct professional education activities on the latest treatment guidelines for high blood pressure, cholesterol, and heart attacks. For public education, the NHLBI is mounting several community-based efforts using mass media to position CHD and its risk factors as major health issues in the African American community. Educational interventions involve Historically Black Colleges and Universities (HBCU), churches, and community mobilization of coalitions and other groups such as sororities and fraternities to increase awareness, prevention and control of CHD and its risk factors in African American communities.

NHLBI has also taken action steps to develop and implement a Latino Community Cardiovascular Disease (CVD) Prevention and Outreach Initiative. The first project will begin in the Washington, D.C. metropolitan area. Widespread community involvement in the endeavor has been emphasized through the establishment of a Community Alliance Working for Heart health. The Alliance is made up of Latino health care professionals, community leaders, community-based organization, community educators, churches, clinics and health centers as well as Latino businesses and media who are participating as partners with the NHLBI to plan and implement the project in the community.

The NHLBI has awarded contracts to State health departments in 11 States, Alabama, Arkansas, Georgia, Indiana, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia, that make up the "Stroke Belt" to reduce the risk of stroke in African American communities. Early indications are that the State health departments are carrying out effective stroke risk factor reduction activities in the community and in health care facilities.

Minority populations are also disproportionately affected by asthma. In fact, in some young age groups mortality is three to six times higher, particularly for the African American population. The NAEPP has mounted a multifaceted approach to target the African American and Hispanic populations including mass media campaign, development of emergency department guidelines for use in inner cities, and educational materials based on "lessons learned" from research conducted with minority populations. The media campaign is directed at African Americans and Hispanics with undiagnosed asthma.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten to fifteen years, explain.

Dr. Lenfant: At the request level, the estimated success rate for NHLBI competing research project grants would be approximately 19% in FY 1996. This compares to success rates over the last 15 years of 26.9% in FY 1980, 34.9% in FY 1984, 25.7% in FY 1989, and 23.0% in FY 1994. However, because the NIH has changed slightly the way in which grants are grouped or aligned these data are not entirely comparable.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period?

Dr. Lenfant: In the last 15 years, the average cost of a competing research project grant has increased as follows: FY 1980--$112,900; FY 1984--$140,600; FY 1989--$214,500; FY 1994--$248,500. The percent increase averaged 6.2% per year between 1980-1984, approximately 10.5% per year between 1985-1989, and 3.18% per year between 1989-1994. However, because the NIH has changed slightly the way in which grants are grouped or aligned these data are not entirely comparable.

Mr. Stokes: What is the trend in terms of constant dollars?

Dr. Lenfant: During the same time period, the average cost of a research project grant in constant dollars has increased approximately 4.3% in fifteen years after adjustments for inflation. The largest annual increases in average cost occurred between 1980-1989, with an increase of approximately 1.3% per year. During the five year period from 1989 to 1994, the average cost of a grant decreased 6.6% in constant dollars.

Mr. Stokes: What are the success rates for research applications received from minority researchers, from women, from African Americans, and from HBCUs?

Dr. Lenfant: The data requested are difficult to gather since information on race and gender are identified as optional on NIH grant applications. On the average, approximately 5 percent of NHLBI grant applicants did not provide this information and were coded in the "unknown" category. In FY 1994, however, 25 percent of the applicants chose not to provide this information, which makes it difficult to draw firm conclusions.

The success rates for competing research project grants for minority researchers, women, and Historically Black Colleges and Universities (HBCUs) are shown below for the past ten years. The category "unknown" represents success rates for applications on which race could not be determined.

	1984		1989		1994	
Categories	# of Appl.	Success Rates	# of Appl.	Success Rates	# of Appl.	Success Rates
Minority researchers:						
Asians	213	28.6%	231	18.2%	227	18.9%
African Americans	19	36.8	27	18.5	28	10.7
Hispanics	33	33.3	33	36.4	42	14.3
Native Americans	3	0.0	1	100.0	4	0.0
White	1965	35.5	2069	26.4	1775	23.3
Unknown	91	35.2	85	30.6	725	26.1
Women	255	36.5	337	27.3	449	23.6
HBCUs	268	6.3	11	0.0	14	14.3

In addition to competing research project grants awarded to minority researchers, the NHLBI also funded a number of Minority Investigator Research Supplements (MIRS) which are not reflected in the success rate data above. Since the program was initiated in 1988, NHLBI funding increased from 13 supplements for $485 thousand to 182 awards for $6.8 million in FY 1994.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women, to minority researchers, to African American researchers, and to HBCUs?

Dr. Lenfant: The average cost of competing research project grants awarded to minority researchers, women, African Americans and HBCUs in current and constant dollars are shown on the following tables. The category designated as "unknown" represents the average cost of competing grants for applications on which race could not be determined.

	1984	1989	1994
Current Dollars			
Minority researchers:			
Asians	$130,330	$145,514	$204,607
African Americans	120,163	315,536	215,551
Hispanics	304,462	244,352	187,569
Native Americans	0	154,685	0
White	138,594	229,481	275,404
Unknown	233,984	262,789	295,488
Women	103,455	198,748	244,667
HBCUs	53,347	0	246,770

	1984	1989	1994
Constant (1984) Dollars			
Minority researchers:			
Asians	$130,330	114,039	129,253
African Americans	120,163	247,285	136,166
Hispanics	304,462	191,499	118,490
Native Americans	0	121,226	0
White	138,594	179,844	173,844
Unknown	233,984	205,947	186,663
Women	103,455	155,759	154,559
HBCUs	53,347	0	155,888

FTE FREEZE

Mr. Stokes: Is the Institute currently under a FTE freeze, and if so, how long has it been under this freeze?

Dr. Lenfant: The Public Health Service (PHS) imposed a freeze on hiring outside PHS on December 8, 1993, and only recently (February, 1995) allowed such hiring to resume. Thus, NHLBI is in a position to provide factual data on its impact.

o Because a freeze has its largest impact on those occupations that have the largest attrition rates, NHLBI's largest losses came from the intramural research program and, more specifically, science occupations. For example, NHLBI lost 21% of its scientific staff during this one year.

o It takes 6 to 9 months to recruit someone to fill key positions. When the freeze was in effect, NHLBI staff were very reluctant to begin this complicated process when it was not clear that the selecting official could make an offer once the best candidate was identified. Thus, key positions stayed vacant for prolonged periods.

o Because of the rapid decrease in employment, the NHLBI is now trying to re-establish equilibrium and replace key personnel to minimize negative program impact. At the same time, the Institute has initiated several efforts to streamline processes, and to re-engineer the way in which our work is performed. In this way, we can accommodate FTE reductions in a more orderly and rational fashion.

FEDERAL ROLE IN INTRAMURAL RESEARCH

Mr. Stokes: In light of continuing fiscal restraints, in your professional judgement, why must the federal role in intramural research continue?

Dr. Lenfant: There are a number of important reasons:

- o the ability to quickly initiate research projects to respond to new and unexpected public health crises;

- o the necessity for long-term, uninterrupted support to assure that certain areas of research can produce the expected payoff;
- o the opportunity to support significant high potential research not funded elsewhere;
- o the close proximity of basic research laboratories and clinical programs, which encourages scientific collaboration in a clinical setting--the earliest gene therapy research is a superb example;
- o the unique content of the clinical research programs;
- o the large confluence of scientific expertise in a single geographic area;
- o the opportunity for collaboration with the private sector to bring scientific advances developed by the federal government to the general populace expeditiously;
- o the outstanding research training provided to the next generation of biomedical (especially clinical) scientists; and
- o the opportunity to continue a fertile research environment that has produced a number of extraordinary past achievements;

The research staff of NHLBI's research program includes 6 members of the prestigious National Academy of Scientists, including one Nobel Laureate, and many other scientists who are at the leading edge of their respective fields. All of the scientific staff is engaged essentially full time in research with only relatively minor administrative responsibilities other than those directly related to research.

The intramural program is particularly valuable for its clinical research, not only because of the large number of beds devoted to full time research but also because of the intimate relationship between clinical research and basic research on which progress in clinical research depends. Not only are there extensive interactions between the clinical and non-clinical scientists but each of the clinical branches itself conducts extensive laboratory-based research. This brings the findings of the laboratory rapidly to the patient's bed. One timely example is the active patent portfolio in gene therapy, including a recently issued patent, which has been licensed to a small U.S. biotechnology company. Another current example, is the fruitful interaction of basic scientists who are pushing the frontier of the clinical applications of magnetic resonance imaging.

HEART ATTACK IN WOMEN

Ms. Lowey: Could you discuss what advances your institute has made against heart attack in women?

Dr. Lenfant: Over the past several decades, research conducted and supported by the NHLBI has resulted in remarkable improvements in our ability to diagnose, treat, and prevent heart attack. Widespread awareness and control of high blood pressure and high blood cholesterol, favorable trends in abstinence from smoking, the advent of thrombolytic ("clot busting") therapy to abort heart attacks in progress, and development of coronary artery bypass surgery and balloon angioplasty to open occluded blood vessels exemplify the progress that has been made. These advances have improved survival in women, as well as in men, as witnessed by the fact that coronary heart disease (CHD) death rates for both genders declined more than 50 percent during the past 25 years.

Let me mention two recent clinical trials that produced findings of particular relevance to heart attack in women. The Systolic Hypertension in the Elderly Program evaluated the benefits of treating isolated systolic hypertension, a form of high blood pressure that affects many older women. It found that treatment with inexpensive, commonly used drugs for a 5-year period reduced rates of CHD, including heart attack, by 27 percent. The Postmenopausal Estrogen/Progestin Interventions trial assessed the effects of several regimens of hormone replacement therapy (HRT) on risk factors for CHD in postmenopausal women. The trial found that HRT raised levels of beneficial HDL cholesterol, and lowered levels of harmful LDL cholesterol and fibrinogen, a blood clotting factor predictive of heart attack. The results of this study provide scientifically based guidance for postmenopausal women and their physicians seeking safe hormonal regimens that will improve their CHD risk factors.

Ms. Lowey: What additional research opportunities are there in this area?

Dr. Lenfant: Building upon a solid foundation of basic and clinical research, the Institute has identified a number of unanswered questions that represent new research opportunities. Selected examples include the following:

Why do chest pain syndromes occur frequently in women in the absence of demonstrable coronary atherosclerotic obstruction?

Why are initial heart attacks more frequently fatal in women? Why do women experience an excess of congestive heart failure and a less favorable response to coronary artery bypass surgery?

Does HRT reduce the incidence of CHD in postmenopausal women? What are the mechanisms by which estrogen exerts its influence on CHD?

What is the mechanism by which diabetes increases risk of cardiovascular disease in women?

Does lowering blood pressure in older women confer protection against stroke and heart disease?

Are serum cholesterol and other lipid measures predictive of CHD in older women? Are cholesterol-lowering regimens safe and effective for older women?

What are the differential effects of anticoagulants as a function of gender, age, and premenopausal or postmenopausal status?

How do hemostatic parameters vary as a function of gender and premenopausal or postmenopausal status?

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

FY 1996 Budget .... Page No.

Organization chart 140

Appropriation language 141

Amounts available for obligation 143

Budget mechanism table 144

Summary of changes 146

Budget authority by object 148

Administrative costs 150

Significant items in House and Senate Appropriations Committee reports 151

Authorizing legislation 155

Appropriation history 156

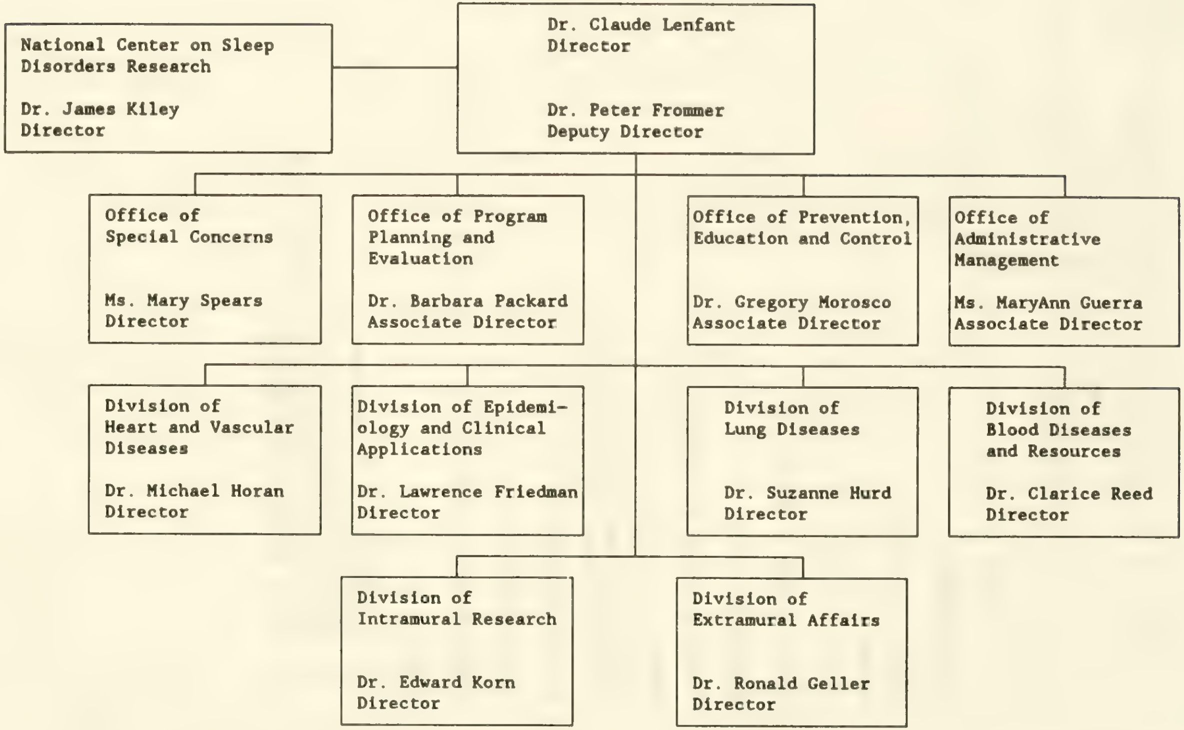
Budget authority by activity 158

Justification:

A. General statement 159
B. Extramural research programs 162
C. Intramural research 173
D. Research management and support 177
E. Detail of full-time equivalent employment (FTE) 181
F. Detail of end-of-year employment 182

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute
Organization Structure



Dr. Claude Lenfant
Director

Dr. Peter Frommer
Deputy Director

National Center on Sleep Disorders Research

Dr. James Kiley
Director

Office of Special Concerns

Ms. Mary Spears
Director

Office of Program Planning and Evaluation

Dr. Barbara Packard
Associate Director

Office of Prevention, Education and Control

Dr. Gregory Morosco
Associate Director

Office of Administrative Management

Ms. MaryAnn Guerra
Associate Director

Division of Heart and Vascular Diseases

Dr. Michael Horan
Director

Division of Epidemiology and Clinical Applications

Dr. Lawrence Friedman
Director

Division of Lung Diseases

Dr. Suzanne Hurd
Director

Division of Blood Diseases and Resources

Dr. Clarice Reed
Director

Division of Intramural Research

Dr. Edward Korn
Director

Division of Extramural Affairs

Dr. Ronald Geller
Director

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung and Blood Institute

For carrying out section 301 [and 1105] and title IV of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases, and blood and blood products, [$1,259,590,000] *$1,294,456,000*. 1/

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

1/ Includes $15,360,000, included in the President's Budget Appendix, for the National Bone Marrow Registry which has been transferred to the Health Resources and Services Administration.

NATIONAL INSTITUTES OF HEALTH

National, Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate 2/
Appropriation	$1,277,880,000	$1,259,590,000	$1,294,456,000
Section 205 Procurement reduction	---	-664,000	---
Section 207 Rent reduction	---	-64,000	---
Section 513 S&E reduction	---	-390,000	---
National Marrow Donor Program redelegation	---	---	-15,360,000
Subtotal, adjusted appropriation	1,277,880,000	1,258,472,000	1,279,096,000
Comparative transfer to: HRSA for the National Marrow Donor Program	-11,171,000	-15,360,000	---
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	-54,977,000	---	---
Comparative transfer to: Other NIH Institutes for Management Fund adjustment	-1,702,000	-1,565,000	---
Subtotal, adjusted budget authority	1,210,030,000	1,241,547,000	1,279,096,000
Unobligated balance, lapsing	-28,000	---	---
Total obligations	1,210,002,000	1,241,547,000	1,279,096,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1994 - $4,395,000; 1995 - $7,000,000; 1996 - $7,000,000.

2/ Excludes $15,360,000, included in the President's Budget Appendix, for the National Bone Marrow Registry which has been transferred to the Health Resources and Services Administration.

Also excludes funding for HIV activities: FY 1995--$55,485,000; FY 1996--$57,925,000, included in the Office of AIDS Research, NIH

Note: Excludes $817,000 for Royalties in FY 1994 and $1,200,000 in FY 1995.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate 1/	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting..........	1,995	$583,483,000	1,846	$564,105,000	1,973	$627,476,000
Admin. suppl..........	(148)	5,311,000	(80)	3,000,000	(80)	3,126,000
Competing						
Renewal.............	231	76,997,000	258	91,446,000	194	71,327,000
New.................	372	90,097,000	425	105,608,000	337	88,458,000
Supplemental........	6	1,144,000	7	1,323,000	5	1,038,000
Subtotal, competing...	609	168,238,000	690	198,377,000	536	160,823,000
Subtotal, res. proj..	2,604	757,032,000	2,536	765,482,000	2,509	791,425,000
SBIR/STTR..............	113	16,753,000	137	23,435,000	133	23,998,000
Total, res. proj.....	2,717	773,785,000	2,673	788,917,000	2,642	815,423,000
Research Centers						
Spec./comp. ctrs......	69	98,536,000	73	103,906,000	73	103,906,000
Other research						
Res. career program...	359	30,321,000	362	32,213,000	358	32,884,000
Coop. clin. research..	20	11,121,000	23	11,191,000	23	11,393,000
Minority biom. res....		2,434,000		2,753,000		2,803,000
Other res. related....	43	7,623,000	43	7,838,000	59	7,979,000
Subtotal, other res.....	422	51,499,000	428	53,995,000	440	55,059,000
Total, research grants....	3,208	923,820,000	3,174	946,818,000	3,155	974,388,000

Training						
Individual awards:						
Noncompeting..........	112	3,443,000	107	3,288,000	116	3,790,000
Competing.............	130	3,819,000	121	3,952,000	107	3,580,000
Subtotal, individual....	242	7,262,000	228	7,240,000	223	7,370,000
Institutional awards:						
Noncompeting..........	1,232	33,560,000	1,153	34,528,000	1,152	35,687,000
Competing.............	237	7,426,000	209	6,477,000	183	6,056,000
Subtotal, institutional.	1,469	40,986,000	1,362	41,005,000	1,335	41,743,000
Total, training...........	1,711	48,248,000	1,590	48,245,000	1,558	49,113,000
Research & development contracts...............	158	82,749,000	173	91,617,000	169	95,113,000
	FTEs		FTEs		FTEs	
Intramural research.......	396	98,583,000	402	96,873,000	402	100,737,000
Research management and support.............	456	56,630,000	455	57,994,000	445	59,745,000
Extramural construction...		---		---		---
Total.....................	852	1,210,030,000	857	1,241,547,000	847	1,279,096,000
(Clinical Trials).......		(96,491,000)		(99,800,000)		(105,000,000)

1/ Excludes $15,360,000, included in the President's Budget Appendix, for the National Bone Marrow Registry which has been transferred to the Health Resources and Services Administration.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Summary of Changes

1995 Estimated budget authority	$1,241,547,000
1996 Estimated budget authority	1,279,096,000 1/
Net change	+37,549,000

	1995 Current Estimate Base		Change from base	
	FTEs	Amount	FTEs	Amount
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase		$28,834,000		+$346,000
b. Annualization of January 1995 pay raise		28,834,000		+110,000
c. One more day of pay		28,834,000		+110,000
d. January 1996 pay increase		28,834,000		+450,000
e. Service and Supply fund increase		9,012,000		+261,000
f. Payment for centrally furnished services		35,924,000		+415,000
g. Increased cost of laboratory materials and other supplies		21,788,000		+666,000
h. FTS decrease		421,000		-93,000
i. DHHS Working Capital fund		894,000		-23,000
Subtotal				+2,242,000
2. Research Management and Support				
a. Within grade increase		29,643,000		+412,000
b. Annualization of January 1995 pay raise		29,643,000		+116,000
c. One more day of pay		29,643,000		+114,000
d. January 1996 pay increase		29,643,000		+485,000

Summary of Changes--continued

e. Unemployment compensation and FECF.............	271,000	+8,000
f. Service and Supply fund increase........	2,005,000	+58,000
g. Payment for centrally furnished services...	11,620,000	+665,000
h. Increased cost of laboratory materials and other supplies...	14,726,000	+428,000
Subtotal...........		+2,286,000
Total, Built-in..		+4,528,000

	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.........	1,846	567,105,000	+127	+63,497,000
b. Competing............	690	198,377,000	-154	-37,554,000
c. SBIR/STTR............	137	23,435,000	-4	+563,000
Total................	2,673	788,917,000	-31	+26,506,000
2. Research centers...........	73	103,906,000	--	---
3. Research career program....	362	32,213,000	-4	+671,000
4. Coop. Clinical research....	23	11,191,000	--	+202,000
5. Minority biom. research....	--	2,753,000	--	+50,000
6. Other research related.....	43	7,838,000	+16	+141,000
7. Research training..........	1,590	48,245,000	-32	+868,000
8. Research and development contracts................	173	91,617,000	-4	+3,496,000

	(FTEs)	Amount	(FTEs)	Amount
10. Intramural research........	402	96,873,000	--	+1,622,000
11. Research management and and support..............	455	57,994,000	-10	-535,000
Subtotal, Program........				+33,021,000
Total changes..........				+37,549,000

1/ Excludes $15,360,000, included in the President's Budget Appendix, for the National Bone Marrow Registry which has been transferred to the Health Resources and Services Administration.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment	857	847	-10
Full-time equivalent of overtime and holiday hours	4	4	---
Average SES salary	$111,345	$113,030	+$1,685
Average GM/GS grade	10.42	10.30	-0.12
Average GM/GS salary	45,774	46,323	+549
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	74,314	75,540	+1,226
Average salary of ungraded positions	35,150	35,730	+580
Personnel compensation:			
Full-time permanent	$34,685,000	$35,302,000	+$617,000
Other than full-time permanent	6,788,000	6,798,000	+10,000
Other personnel compensation	1,976,000	2,012,000	+36,000
Special personnel service payments	4,245,000	4,322,000	+77,000
Total personnel compensation	47,694,000	48,434,000	+740,000
Personnel benefits	10,524,000	10,743,000	+219,000
Benefits for former personnel	259,000	265,000	+6,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Travel and transportation of persons....................	1,139,000	1,166,000	+27,000
Transportation of things........	228,000	233,000	+5,000
Rental payments to GSA..........	3,000	3,000	---
Rental payments to others.......	633,000	648,000	+15,000
Communications, utilities, and miscellaneous charges.........	2,969,000	2,944,000	-25,000
Printing and reproduction.......	1,145,000	1,171,000	+26,000
Consulting services.............	847,000	866,000	+19,000
Other services..................	14,265,000	14,436,000	+171,000
Purchases from government accounts......................	64,503,000	68,660,000	+4,157,000
Operation of GOCOs..............	---	---	---
R&D Contracts...................	88,757,000	92,187,000	+3,430,000
Supplies and materials..........	9,253,000	9,475,000	+222,000
Equipment.......................	4,050,000	4,144,000	+94,000
Lands and structures............	5,000	5,000	---
Grants, subsidies, & contributions...............	995,063,000	1,023,501,000	+28,438,000
Insurance claims and indemnities...................	205,000	210,000	+5,000
Interest and dividends..........	5,000	5,000	---
Total adjusted budget authority by object.........	1,241,547,000	1,279,096,000	+37,549,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Administrative Costs

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$34,685,000	$35,302,000	+$617,000
Other than Full-Time Permanent (11.3)	6,788,000	6,798,000	+10,000
Other Personnel Compensation (11.5)	1,976,000	2,012,000	+36,000
Special Personal Service Payments (11.8)	4,245,000	4,322,000	+77,000
Total Personnel Compensation (11.9)	47,694,000	48,434,000	+740,000
Civilian Personnel Benefits (12.1)	10,524,000	10,743,000	+219,000
Benefits for Former Personnel (13.0)	259,000	265,000	+6,000
Travel (21.0)	1,139,000	1,166,000	+27,000
Transportation of Things (22.0)	228,000	233,000	+5,000
Rental Payments to Others (23.2)	633,000	648,000	+15,000
Communications, Utilities, and Miscellaneous Charges (23.3)	2,969,000	2,944,000	-25,000
Printing and Reproduction (24.0)	1,145,000	1,171,000	+26,000
Consulting Services (25.1)	847,000	866,000	+19,000
Other Services (25.2)	14,265,000	14,436,000	+171,000
Purchases from Government Accounts (25.3)	50,709,000	55,306,000	+4,597,000
Operation of GOCOs (25.4)	---	---	---
Supplies and Materials (26.0)	9,253,000	9,475,000	+222,000
Total	139,665,000	145,687,000	+6,022,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1995 House Report	
Cystic Fibrosis	
1. The House in its report 103-553, page 47, stated, "The bill provides sufficient funds for NHLBI to continue existing centers. In addition, the Committee urges NIH to consider expanding the centers if resources permit both at NHLBI and NIDDK."	1. The NHLBI will continue to support six centers to study gene therapy approaches to cystic fibrosis treatment.
Behavioral Research	
2. The House in its report 103-553, page 47, stated, "The Committee is pleased to learn that the Institute is increasing its portfolio of research on the relationship between behavior and health since this research has significant public health implications. The Committee encourages the Institute to pursue these and other behavioral research activities to the extent that funds permit."	2. The Institute has recognized the importance of the relationship between behavior and health; and has increased its support for this area in each of the last several years.
Behavioral Research	
3. The House in its report 103-553, page 47, stated, "The Committee encourages the Institute to fund grants, including a clinical trail if appropriate, in the social support research areas it has identified as priorities."	3. Beginning in FY 1995, the Institute will fund a clinical trial entitled "Enhancing Recovery in Coronary Heart Disease Patients." This trial will evaluate the effects of psychosocial intervention in high risk heart attack patients. The total cost of this 8 year trial is estimated to be $30 million.

Bionutrition

4. The House in its report 103-553, page 48, stated, "The Committee encourages NHLBI to continue its research efforts on the dietary role of antioxidants and cardiovascular health."

4. The NHLBI will continue to support research on the dietary role of antioxidants and cardiovascular health. Research currently underway includes clinical studies of antioxidants that have potential to impede or retard progression of atherosclerosis and the impact of dietary factors on lipid metabolism, hypertension, clotting factors, and pulmonary status.

Ischemia Heart Disease in Women

5. The House in its report 103-553, page 48, stated, "The Committee encourages the Institute to begin research to improve the reliability of diagnostic tests and to develop safe, efficient and cost-effective diagnostic approaches for evaluating women with chest pain."

5. The Institute plans to fund an initiative to improve the diagnostic reliability of cardiovascular testing in evaluation of ischemia heart disease in women. This initiative will include an assessment of innovative approaches to this very important problem.

Comprehensive Center

6. The House in its report 103-553, pages 48-49, stated, "The Committee encourages the Institute to consider the utility of establishing a comprehensive research and demonstration center for heart, blood vessel, lung, and blood diseases. The Director should be prepared to testify at next year's hearings on the feasibility and priority for such a center."

6. The NHLBI is currently considering the utility and feasibility of establishing a comprehensive research and demonstration center for heart, blood vessel, lung, and blood diseases. The Director, NHLBI, will be prepared to testify on this topic at the appropriations hearings.

Thrombosis

7. The House in its report 103-553, page 49, stated, "The Committee is encouraged by the recent advances in research on thrombosis, in particular the application of genetic methods, and urges the Institute to support additional work in this area."

7. Much remains to be done, but the new discoveries about the interactions of hereditary and environmental factors that predispose certain individuals to develop thrombi make prospects for improved prevention and treatment of thrombosis very promising. The NHLBI's multidisciplinary approach to both clinical and basic research is designed to take maximum advantage of new knowledge gained from this investment.

Item	Action Taken or to be Taken
1995 Senate Report	
Gene Therapy and Heart Disease	
1. The Senate in its report 103-318, page 74, stated, "The Committee encourages the Institute to consider initiating research to identify mechanisms by which nutrients affect genes necessary for normal heart development. The Committee also encourages the Institute to consider initiating research to advance gene transfer technology and its potential treatment of multifactorial cardiovascular high blood pressure, stroke, and heart enlargement."	1. The Institute will support a new program in FY 1995 entitled "Gene-Nutrient Interactions in the Pathogenesis of Congenital Heart Defects" to foster basic research on the relationship between genes and nutrients in the etiology and prevention of congenital cardiovascular malformations. A program of Specialized Centers of Research (SCOR) for the Genetics of Hypertension has been announced and awards will be made in 1995. The program goal is to identify and map the genes responsible for hypertension in humans and animals, and clarify the role for specific genetic mutations on the development and maintenance of high blood pressure.
Behavioral Cardiology SCOR	
2. The Senate in its report 103-318, page 74, stated, "Cardiovascular behavioral medicine is uniquely suited to mechanisms like the multidisciplinary SCOR approach, and to the SCOR program's goal of advancing basic knowledge to generate the most effective techniques and methods of clinical management and prevention of heart disease. The Committee reiterates its support for this research and encourages NHLBI to fund a behavioral cardiology SCOR consistent with its commitment to the behavioral sciences."	2. Given competing research priorities, a special center of research in behavioral cardiology is difficult to do at this time. In addition, there is not a consensus within the research community that the SCOR mechanism is the best approach to use in addressing research needs in this area. The Institute is increasing its behavioral research portfolio. For example, beginning in FY 1995, the Institute will fund a clinical trial entitled "Enhancing Recovery in Coronary Heart Disease Patients". This trial will evaluate the effects of psychosocial intervention in high risk heart attack patients. The total cost of this 8 year trial is estimated to be $30 million.

Asthma

3. The Senate in its report 103-318, pages 74-75, stated, "The Committee urges continued support for the Childhood Asthma Management Program that compares therapeutic agents in the treatment of asthma in a prospective long-term manner."	3. The Childhood Asthma Management Program (CAMP) is an 8 year 9 month contract program that began in 1991. It is expected to cost $49.7 million over the study period and will be supported for its full term.

Transfusion Medicine

4. The Senate in its report 103-318, page 75, stated, "Given the importance of improving the safety of our Nation's blood supply, the Committee encourages the Institute to create a specialized center of research in transfusion medicine. The Committee is supportive of research that would further improve the safety and efficacy of transfusion medicine therapy."	4. The NHLBI supports an ongoing program of specialized centers of research (SCOR) in transfusion medicine to expedite development and application of new knowledge essential for improved safety, efficacy, and availability of blood, blood components, blood derivatives, blood substitutes, and transplant materials. A new competition for this centers program is proceeding under a new initiative that encourages use of new and innovative technologies to pursue fundamental research in transfusion biology, as well as clinical investigations in transfusion medicine. The new centers have an expected start date of January 1996.

Comprehensive Center

5. The Senate in its report 103-318, page 76, stated, "The Committee encourages the Institute to consider the utility of establishing a comprehensive research and demonstration center for heart, blood vessel, lung, and blood diseases. The Director should be prepared to testify at next year's hearings on the feasibility and priority of such a center."	5. The NHLBI is currently considering the utility and feasibility of establishing a comprehensive research and demonstration center for heart, blood vessel, lung, and blood diseases. The Director, NHLBI, will be prepared to testify on this topic at the appropriations hearings.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Authorizing Legislation

	PHS ACT/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation........	Section 301	42§241	Indefinite	>$1,193,302,000	Indefinite	>$1,229,983,000
National Heart, Lung, and Blood Institute..	Title IV, Parts B and C	42§284c	Such sums as necessary		Such sums as necessary	
National Research Service Awards.......	Section 487(d)	42§288	Such sums as necessary	48,245,000	Such sums as necessary	49,113,000
Total Adjusted Budget Authority.....				1,241,547,000		1,279,096,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Appropriation History

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	$785,697,000	$921,410,000	$921,502,000	$930,001,000
1988	821,887,000	990,808,000 3/	990,646,000	965,536,000
1989	1,015,471,000 4/	1,018,903,000	1,056,603,000	1,045,985,000
1990	1,039,846,000 5/	1,090,930,000	1,091,597,000	1,087,524,000 6/
1990 Sequester				(15,170,000)
1991	1,112,502,000	1,135,589,000 7/	1,137,235,000	1,126,942,000 8/
1991 Sequester				(15,000)
1992	1,209,924,000	1,202,398,000	1,190,396,000	1,188,593,000 9/
1993	1,245,396,000	1,228,455,000	1,228,455,000	1,214,793,000 10/
1994	1,198,402,000	1,277,880,000	1,277,880,000	1,277,880,000
1995 11/	1,266,961,000	1,259,590,000	1,259,590,000	1,258,472,000 12/
1996 11/	1,279,096,000 13/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $17,091,000 for NHLBI.

3/ Does not include funding for AIDS research consolidated at the Secretary's level.

4/ Excludes funds for AIDS research and education ($39,032,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ The 1990 request excludes funds for the National HIV program ($42,651,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of $3,740,000.

7/ Excludes $44,476,000 in NRSA training programs not considered.

8/ Excludes Section 514 reductions of $31,708,000.

9/ Excludes Section 214 and 513 reductions of $9,398,000 and enacted rescission of $1,407,000.

10/ Excludes Section 215, 511, and 513 reductions of $13,662,000.

11/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

12/ Excludes procurement reform, rent, and salary and expense reductions of $1,118,000.

13/ Excludes $15,360,000, included in the President's Budget Appendix, for the National Marrow Donor Registry which has been transferred to the Health Resources and Services Administration.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate 1/		Change	
Extramural Research:	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTE	Amount
Heart and vascular diseases program	--	$607,987	--	$620,804	--	$636,614	--	$660,651	--	$679,857	--	+$19,206
Lung diseases program	--	191,146	--	203,938	--	220,538	--	228,172	--	234,185	--	+6,013
Blood diseases and resources program	--	175,273	--	167,094	--	184,825	--	182,892	--	187,512	--	+4,620
Sleep disorders research program	--	8,850	--	8,898	--	12,840	--	14,965	--	17,060	--	+2,095
Subtotal, extramural	--	983,256	--	1,000,734	--	1,054,817	--	1,086,680	--	1,118,614	--	+31,934
Intramural research	445	91,295	433	92,948	396	98,565	402	96,873	402	100,737	--	+3,864
Research management and support	484	56,880	476	56,719	456	56,620	455	57,994	445	59,745	-10	+1,751
Total, obligations	929	1,131,431	909	1,150,401	852	1,210,002	857	1,241,547	847	1,279,096	-10	+37,549
Unobligated balance, lapsing	--	23	--	47	--	28	--	---	--	---	--	---
Total, adjusted budget authority	910	1,131,454	909	1,150,448	852	1,210,030	857	1,241,547	847	1,279,096	-10	+37,549

1/ Excludes $15,360,000, included in the President's Budget Appendix, for the National Bone Marrow Registry which has been transferred to the Health Resources and Services Administration.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTES are included in the NIH Office of AIDS Research.

Justification

National Heart, Lung, and Blood Institute

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
852	$1,210,030,000	857	$1,241,547,000	847	$1,279,096,000	-10	+$37,549,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national research program to prevent, diagnose, treat, and cure heart, blood vessel, lung and blood diseases, and sleep disorders; and to provide for an adequate and safe blood supply for the Nation. To achieve these goals, the Institute supports a comprehensive program of basic and clinical investigations, clinical trials, epidemiologic studies, and demonstration and education projects. This multifaceted approach has led to significant advances against several of the leading causes of death, and opened new and exciting avenues of research that could prevent these diseases and disorders. Such progress holds promise for improved quality of life for the American public and a reduction in the enormous impact these diseases have on the health care system.

The Institute has several scientific advances to report, which are delineated in the sections that follow. In addition to these research advances, the NHLBI continues to identify future research opportunities and develop initiatives to take advantage of emerging areas of science, to fill gaps in our understanding of certain areas, or to stimulate new ideas in areas where progress has slowed and fresh approaches are needed.

Thus, the Institute will support new initiatives in such basic research areas as molecular genetics of hypertension; gene nutrient interactions; angiogenesis in breast cancer; hematopoietic stem cell biology; and stem cell sources. New clinical or population based initiatives include insulin, insulin resistance, and cardiovascular disease; physical activity and cardiovascular health, ischemic heart disease in black Americans and women; innovative ventricular assist systems; enhancing recovery in coronary heart disease patients; atrial fibrillation management; interventions to improve asthma management in schools; mechanisms of post bone marrow transplantation lung injury; and blood coagulation in sickle cell disease.

For the first time the Institute is showing a specific budget amount for the recently established National Center on Sleep Disorders Research. This Center brings exciting prospects to the research portfolios of NHLBI, as well as several other Institutes at NIH. The Center's first initiative will focus on the cardiopulmonary aspects of sleep apnea. This initiative will determine the degree to which sleep apnea serves as a risk factor for the development of cardiovascular and cerebrovascular disease. It will also examine possible associations between sleep apnea, hypertension, and stroke among different age, gender, and ethnic groups. The Center is also actively pursuing its legislative mandate to develop a research plan.

The Institute continues to carry out its important and highly regarded education programs and initiatives. For example, a strategy development conference in June 1994 has helped identify priorities in educating the public, patients, and health professionals regarding sleep and sleep disorders. The results of the workshop will form the basis for sleep disorders professional and public education initiatives in the next few years. Also the National Asthma Education Program has developed a report on the cost effectiveness, quality, and financing of asthma care. The Institute also began a Latino Community Cardiovascular Disease Prevention and Outreach Initiative. Finally, the NHLBI has worked with the Office of Minority Health here at NIH to develop an initiative to address the disparity in the knowledge about coronary heart disease symptoms, risk factors, and methods of prevention between black and white Americans. A key component of this initiative will be carried out in conjunction with Historically Black Colleges and Universities.

The President's appropriation request of $1,279,096,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NHLBI during the last five years has been as follows:

	Amount	FTEs
FY 1991	$1,067,946,000	898
FY 1992	1,131,454,000	929
FY 1993	1,150,448,000	909
FY 1994	1,210,030,000	852
FY 1995	1,241,547,000	857

Purpose and Method of Operation

The Institute organizes its research efforts around the major disease groupings for which it has responsibility. The Institute's Heart and Vascular Diseases Program, Lung Diseases Program, Blood Diseases and Resources Program, and Sleep Disorders Program support research throughout the United States. The Institute also has a very active Intramural Research program in which Government scientists conduct important and cutting edge biomedical research of all types. All of these programs are augmented by the activities of the Office of Prevention, Education, and Control.

All NIH components utilize similar mechanisms. Mechanisms utilized by the NHLBI include research project grants, specialized centers of research and comprehensive research centers, several types of research career awards, cooperative clinical research, demonstration and education research, research training, research contracts, and research conducted by NHLBI intramural scientists.

Overall Budget Policy

The FY 1996 budget request for the National Heart, Lung, and Blood Institute is $1,279,096,000, an increase of $37,549,000 over the FY 1995 comparable appropriation level of $1,241,547,000.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The request includes $815,423,000 for 2,642 research project grants in FY 1996, compared to $788,917,000 for 2,673 grants supported in FY 1995.

At the request level, the Institute will support 73 research centers, 358 research career awards, 59 other research related awards, 23 cooperative clinical research grants, and 1,558 individual and institutional full-time-training positions. An increase of $50,000 is provided for minority biomedical research.

The request includes $95,113,000 for 170 research and development contracts, an increase of $3,496,000 over the FY 1995 level.

In intramural research, the FY 1996 budget includes $100,737,000 and 402 FTEs, an increase of $3,864,000 over the FY 1995 level. This includes targeted increases in gene therapy and clinical center training programs. In research management and support, the request includes $59,745,000 and 445 FTEs, an increase of $1,751,000 and a decrease of 10 FTEs from the FY 1995 level. Targeted increases are included for the communications infrastructure and prevention education programs.

National Heart, Lung, and Blood Institute

EXTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$1,054,817,000	$1,086,680,000	$1,118,614,000	+$31,934,000

The major extramural programs, that is, those programs for which the Institute provides support but the research is actually conducted elsewhere, are the Heart and Vascular Diseases Program, the Lung Diseases Program, the Blood Diseases and Resources Program, and the Sleep Disorders Program. Extramural funding mechanisms utilized by the NHLBI include research projects grants, specialized centers of research and comprehensive research centers, several types of research career awards, cooperative clinical research, demonstration and education research, research training, and research contracts.

Funding for extramural programs during the last five years has been as follows:

	Amount
FY 1991	$ 928,259,000
FY 1992	983,279,000
FY 1993	1,000,781,000
FY 1994	1,054,817,000
FY 1995	1,086,680,000

Rationale for the Budget Request

The FY 1996 budget request for the extramural research program is $1,118,614,000, an increase of $31,934,000 over the 1995 level of $1,086,680,000. The following materials are examples of recent advances and illustrates the research opportunities that can be pursued with this budget request.

Heart and Vascular Diseases

Hormone Replacement Therapy and Heart Disease Risk Factors

The Postmenopausal Estrogen/Progestin Interventions (PEPI)--the first major clinical trial to examine the effects of sex hormones on heart disease risk factors in postmenopausal women--found that all four of the hormonal regimens tested produced significant increases in levels of HDL cholesterol. For women, a high level of HDL is believed to provide strong protection against coronary heart disease (CHD). Although estrogen taken alone and estrogen combined with micronized (natural) progesterone yielded the greatest increases in HDL, the two other estrogen/progestin combinations tested also compared favorably with a placebo. The PEPI study also found that, compared with the placebo, all of the active treatments caused significant decreases in LDL ("bad") cholesterol and fibrinogen, a blood clotting factor predictive of stroke and heart attack. Furthermore, neither estrogen taken alone nor estrogen/progestin combinations increased blood pressure, as had been previously believed.

Study participants who had not had a hysterectomy underwent annual biopsies to detect cell overgrowth in the uterine lining, a potentially precancerous condition. Although none of the three estrogen/progestin combinations caused this condition, over half of the women taking estrogen alone experienced it. These results indicate that combination hormonal therapy may be the preferred treatment for women who still have a uterus. The results of the PEPI study provide scientifically based guidance for postmenopausal women and their physicians seeking safe hormonal regimens that will improve their heart disease risk factors. Although the intervention phase of the trial is now complete, study participants will be followed for an additional 3 years to ensure that no untoward effects occur as a result of their participation in this clinical trial.

Coronary Heart Disease in Blacks

Research on CHD has contributed to the decline in cardiovascular disease morbidity and mortality that has occurred during the past 3 decades in the United States. However, life expectancy and rates of illness and death from CHD have not improved as much for blacks as for whites. Available data indicate that the probability of dying from CHD is greater in black Americans than in white Americans, and that there is a higher prevalence among blacks of smoking, hypertension, diabetes, obesity, and left ventricular hypertrophy. To address disparities in prevention, diagnosis, treatment, and outcomes of CHD, the NHLBI convened a Working Group on Research in Coronary Heart Disease in Blacks. The group assessed the state of the science and identified scientific opportunities in basic, clinical, and behavior and prevention research. In response to their recommendations, the Institute has launched a new program, Specialized Centers of Research in Ischemic Heart Disease in Blacks. Its goals are to advance understanding of the expression of heart disease in blacks through exploitation of modern methods and approaches to molecular biology, cellular and organ physiology, and clinical practice. Special emphasis will be placed on sudden cardiac death, microvascular disease, diabetic heart disease in the expectation that new knowledge in these areas will ultimately reduce the burden of CHD in this population.

Genetic Basis of Essential Hypertension

Recent application of modern molecular genetic techniques to the study of hypertension has led to some startling discoveries about the genetic basis of this multifaceted disorder. Whether gene mapping is conducted in animals or humans, it is becoming clear that a complex array of genes interacting with each other and with environmental factors lead to hypertension. A newly discovered gene, the S_A gene, has been linked to essential hypertension in specific animal models and in certain human populations. However, studies show that genetic causality for the condition is complex and will vary among different populations and within the same population exposed to different environmental factors. The Institute will continue to support research that will ultimately enable clinicians to identify subgroups of the hypertensive population and provide tailored treatment and preventive regimens.

Silent Myocardial Ischemia

Although ischemia--deficient blood flow--associated with CHD often manifests itself as angina, many episodes are asymptomatic or "silent." It is estimated that of the approximately 6 million patients with chronic symptomatic CHD, up to 3 million may exhibit silent ischemia. A recent trend toward treating silent ischemia as vigorously as angina has led to widespread application of costly medical and revascularization therapies in the belief that suppression of silent ischemia in patients with CHD will reduce morbidity and improve survival. The Asymptomatic Cardiac Ischemia Pilot study is examining the validity of this hypothesis. Early results of the pilot study indicate that asymptomatic ischemia occurs frequently and can be suppressed in 45 to 55 percent of patients with advanced CHD by revascularization or low or moderate doses of medication, the first being most effective. Whether aggressive suppression of ischemia in patients with CHD will reduce morbidity and improve survival awaits determination in a planned full-scale trial. Its results are expected to provide insights into the cost-effectiveness of therapy for patients with CHD.

Infant Heart Surgery

A recent clinical trial has provided important information that is likely to improve the outcome of surgery for congenital heart disease, a condition that affects about 30,000 U.S. newborns annually. Many infants require open heart surgery within the first 3 months of life for palliation of the structural defects. Two surgical techniques--hypothermic circulatory arrest and low-flow cardiopulmonary bypass--had been widely used but their relative efficacy was not established, and concerns existed that hypothermic circulatory arrest might have adverse effects. A clinical trial was designed to resolve this issue. Results showed that circulatory arrest was associated with greater nervous system perturbation in the early postoperative phase than was found with low-flow bypass. Moreover, 1 year after surgery, patients who were subjected to hypothermic arrest were more likely to have neurological and developmental abnormalities than patients who received low-flow bypass. This information, already disseminated to pediatric surgeons, provides a basis for decisions regarding optimal conditions for surgery and subsequent prognosis.

Ventricular Assist Devices

An experimental, implantable ventricular assist device has been successfully employed in a small number of patients, providing them complete ambulatory freedom to live normally and engage in moderate exercise. Using technology developed by NHLBI-supported research, these electrically powered devices maintained circulation in patients with terminal heart failure who were awaiting suitable donor hearts for transplantation. Currently, heart transplantation is the only recognized form of therapy for the estimated 30,000 to 40,000 Americans who develop end-stage heart failure each year. Many patients who could benefit from such therapy die because of limited donor availability. The nearly complete functional recovery of patients receiving the ventricular assist device is evidence of its success and feasibility as a potential alternative to cardiac transplantation. Current devices are currently designed for 1 to 2 years of use. The NHLBI is beginning a new program to develop cost-effective, innovative ventricular assist systems with 5-year reliability.

Left Ventricular Hypertrophy

According to new results from the Framingham Heart Study, electrocardiograms (ECGs) can help predict the likelihood of a heart attack, stroke, or other cardiovascular event in patients with left ventricular hypertrophy (LVH), a thickening of the muscle of the heart's left chamber. LVH occurs in about 15 to 20 percent of adults, especially older persons and those who have high blood pressure. The study found that regression of LVH, as shown on the ECG, was associated with a decreased likelihood of heart attack, stroke, or other cardiovascular event in both men and women. Although the magnitude of risk reduction depended on the type of ECG change, the risk of cardiovascular events among LVH patients whose ECGs improved was about half that of patients whose ECGs were unchanged. Conversely, patients whose ECGs worsened doubled their risk of cardiovascular events. The study provides important evidence that aggressive high blood pressure treatment appears to improve LVH and is associated with reduced cardiovascular event risk. This finding is expected to lead to improved management of patients with LVH.

Rapid Response to Heart Attack Symptoms

A major new research program has been initiated to assess approaches that reduce the time between onset of symptoms of heart attack and contact with the health care system. Approximately 1.25 million people experience a heart attack and 500,000 people die of CHD in the United States each year. Treatment with thrombolytic ("clot-busting") drugs can reduce mortality by 25 percent if started within the first few hours of symptoms. Many people, however, do not seek care early enough to become candidates for thrombolytic therapy or to benefit from it fully. In the new study, a community-wide educational intervention will be applied in 10 communities. Ten matched communities not receiving the intervention will serve as a comparison group. The study will examine the impact of the intervention on use of emergency medical services, hospital emergency departments, and thrombolytic therapy, as well as on case fatality. The ultimate goal is to develop an effective community education program that can be implemented nationwide to reduce time-to-treatment for heart attack and reduce mortality from CHD.

New Diagnostic Test for Heart Attack

A new enzyme assay has been developed that enables emergency room physicians to diagnose or rule out acute heart attack within the first 6 hours after onset of symptoms, thereby reducing unnecessary admissions to coronary care units (CCUs). Currently, fewer than 30 percent of patients admitted to CCUs are subsequently found to have experienced a heart attack, and it is estimated that the cost of caring for "false alarms" in the CCU is $4 billion per year. The new test is also expected to save lives by facilitating rapid and accurate identification of patients who may benefit from clot-dissolving drugs.

Reducing Dietary Fat Intake in Children

The NHLBI supports a number of research programs focused on issues related to the feasibility, safety, and effectiveness of dietary modification in children. The Dietary Intervention Study in Children, for example, addresses concerns about the safety of fat-reduced diets, especially for children who are in their peak growing years. The study recruited boys and girls, ages 8 to 10 years, who had elevated levels of LDL (the harmful form of cholesterol) and taught them and their families to reduce the youngsters' intake of total fat, saturated fat, and cholesterol. Results showed that a reduced-fat diet is safe, while effective in improving blood cholesterol levels. Approaches to achieving a population-wide reduction in fat intake among children are being explored in two school-based programs. The feasibility phase of the Child and Adolescent Trial of Cardiovascular Health (CATCH) demonstrated that school menus can be modified to lower fat content. The main results of CATCH will provide further information on fat content, nutritional adequacy, and safety of reduced-fat school meals and on participation in the school meal program. PATHWAYS, a study in Native American children, is designing an obesity prevention intervention that includes lowering fat content and monitoring calorie and nutrient adequacy of school meals. Safely reducing children's exposure to dietary total fat, saturated fat, and cholesterol could make an important contribution to the nation's goals of reducing CHD.

Role of Triglycerides in Atherosclerosis

Although excess plasma cholesterol has been firmly established as an artery clogger, the role of another form of lipid, triglycerides, has been the subject of intense debate. Until recently, many studies focused on high levels of the "bad" kind of cholesterol (LDL-cholesterol), an approach that may have masked the potential contribution of triglycerides to elevated heart disease risk. Reports from a new study indicate that when high LDL-cholesterol levels were lowered aggressively with the drug lovastatin, triglycerides continued to contribute to the growth of small to moderate size blockages of blood vessels. Such lesions are considered more dangerous than larger lesions because they are more likely to rupture, block an artery, and lead to heart attack. These findings provide support for the contention that two different types of lipid abnormality can lead to CHD and atherosclerosis: one in which LDL-cholesterol is elevated and another in which an elevated triglyceride level occurs in conjunction with low levels of HDL-cholesterol ("good" cholesterol). The latter type includes people with diabetes. Future research will examine whether the progression of artery disease can be slowed or prevented by lowering triglyceride levels, for example, through diet, physical activity, and weight control.

Lung Diseases

Lung Health Study

Results from the Lung Health Study (LHS) indicate that smoking cessation can reduce chances for development of chronic obstructive pulmonary disease (COPD) in high-risk smokers. The study recruited middle-aged men and women who had evidence of reduced lung function, but no clinical disease, and randomly assigned them to receive a smoking intervention, with or without an inhaled bronchodilator, or usual care. After 5 years of follow up, participants in the smoking intervention program experienced significantly less loss of lung function than persons in the usual-care group. Those who achieved and maintained abstinence from smoking had the smallest declines in lung function. The LHS smoking cessation intervention, which combined state-of-the-art behavioral approaches with a nicotine replacement aid, realized a 5-year sustained quit rate (22 percent) higher than any ever reported in a major study and much higher than that reported for the usual-care group (6 percent). The study also showed that long-term use of a bronchodilator does not change the course of lung function decline in persons at the early stages of disease. Application of the LHS findings can be expected to have a significant impact on personal and financial costs associated with COPD.

Critical Care Medicine

The NHLBI has made a major commitment to assess and respond to the needs for research in critical care. A recently released report from the NHLBI Task Force on Research in Cardiopulmonary Dysfunction in Critical Care Medicine noted that progress in basic science has outpaced other research areas, and advised that increased emphasis be given to clinical research and epidemiological studies. It further recommended that clinical studies be undertaken to examine the validity of definitions used in critical care medicine, to study mechanisms of disease as they manifest themselves in patients, to test the usefulness of a variety of therapeutic modalities, to assess newer modes of mechanical ventilation and the usefulness of various monitoring techniques, and to formulate a better definition of the types of patients who may benefit from intensive care. The report also emphasized the need to develop a cadre of well-trained clinical investigators. In response to a recommendation of the Task Force, the NHLBI awarded contracts to 10 clinical centers and one data and coordinating center to form a network for treatment of patients who have adult respiratory distress syndrome or are at risk of developing it. This network is expected to advance understanding of clinical management issues in critical care medicine and facilitate rapid testing of promising therapeutic strategies.

Dietary Fatty Acids and Smoking-Related Pulmonary Disease

Investigators from the Atherosclerosis Risk in Communities study recently confirmed their hypothesis that smoking-related chronic obstructive pulmonary disease (COPD) is inversely related to dietary intake of n-3 fatty acids, polyunsaturated fatty acids that are abundant in fish. Of the 8,960 study participants who were current or former smokers, seven percent had symptoms of chronic bronchitis, two percent had diagnosed emphysema, and two percent had measurable COPD. N-3 fatty acid intake was estimated from the reported frequency of eating fish such as tuna, salmon, mackerel, swordfish, sardines, bluefish, cod, perch, or catfish. A strong inverse relationship was found between all three categories of COPD described above and n-3 fatty acid intake. The quartile of the population with the highest n-3 fatty acid intake had about one-third the frequency of emphysema and one-half the frequency of chronic bronchitis or measurable COPD of the quartile with the lowest intake. These intriguing observational data suggest that n-3 fatty acids may play a role in the prevention of smoking-related COPD.

Asthma

Recent studies have identified important factors related to development of asthma, wheezing, and allergic reactions. Wheezing associated with lower respiratory tract illnesses is very common in early life, affecting about 20 percent of all children under 1 year of age. Epidemiological studies now indicate the existence of two different wheezing syndromes during early childhood that exhibit completely different risk factors. One, called "early wheezers," is mainly associated with congenitally diminished lung function, but lacks the airways hyperresponsiveness and other risk factors associated with asthma. Two-thirds of the children who wheeze as infants fall into this group and will stop wheezing by age 6, exhibit no further deterioration of lung function, and have a good prognosis. The other syndrome, called "persistent wheezers" and equated with early-onset asthma, is associated with risk factors for asthma, such as increased prevalence of allergic markers precipitated by exposure to high concentrations of allergens early in life, airways hyperresponsiveness, maternal history of asthma, and a significant deterioration of lung function by 6 years of age despite normal levels during the first year of life. These new findings increase our understanding of asthma so that we may not only improve the management and treatment of this disease, but also make progress toward its prevention.

Cystic Fibrosis

Progress continues to be made in the area of gene therapy for cystic fibrosis (CF), and efforts in CF are fueling the entire gene therapy field. Nonetheless, significant obstacles have been encountered that need to be overcome before gene therapy can become a reality. Despite preclinical and clinical studies indicating that adenovirus vectors--gene delivery systems that use the "common cold" virus--for CF can be safe and efficacious, immune responses to these vectors or to CFTR, the CF gene product itself, are limiting their utility as therapeutic agents. Early studies in human subjects suggest that immune responses may account for the limited duration of expression of the genetic information transferred by the adenovirus. This is supported by research that demonstrated prolonged gene expression in immune-deficient strains of mice. A more complete understanding of the immune system is required in order to develop effective and safe gene transfer vectors.

Promising progress is being made with a new vector system, adeno-associated virus (AAV). AAV vectors carrying the CFTR gene have been shown effective in correcting the ion transport abnormalities defective in CF. In preclinical animal studies, there has been no evidence of toxicity, acute or chronic inflammation, or neoplastic change. Moreover, findings suggest that these vectors can successfully deliver the gene to nondividing airway epithelial cells, which is important because under normal circumstances most airway cells are non-dividing. Gene therapy trials in humans using this vector are being planned, and may represent a significant advance in the search for a genetic cure for CF.

Blood Diseases and Resources

Stem Cells From Cord Blood

Blood from placentas and severed umbilical cords has been shown to contain hematopoietic stem cells in sufficient quantities to reconstitute the bone marrow of allogeneic (other than identical twins) transplant recipients. Although highly successful, clinical experience has been mostly limited to grafts between siblings of identical HLA (tissue) type. The Institute is supporting a grant to determine whether a bank of frozen placental bloods, paired with relevant information such as HLA types, numbers of stem cells, and status with regard to certain infectious diseases, is an efficient and cost-effective means of assuring a high probability of finding compatible tissue for fully allogeneic transplantation. Over 3,300 units of placental blood have already been collected, frozen, and stored in the bank. These cells can be made available upon request and offer the advantage of eliminating the delays and uncertainties that now complicate the acquisition of bone marrow from a sibling, another relative, or an unrelated donor. Several placental stem cell transplants, in which placental cells from the bank were used to reconstitute the marrow of patients suffering from leukemia, were performed during the past year with promising results. In view of this preliminary success, the Institute is examining whether developing a network of fetal stem cell banks would facilitate exploration of this new opportunity.

Specialized Centers of Research in Hematopoietic Stem Cell Biology

Research supported by the NHLBI has led to important advances in our ability to isolate and purify hematopoietic stem cells, the precursors of all blood cells. The Institute is now in a strategic position to facilitate rapid transfer of this basic research technology to the bedside. To accomplish this, the NHLBI is planning to implement a new program, Specialized Centers of Research in Hematopoietic Stem Cell Biology. The objectives of this program are to further advance our knowledge of basic stem cell biology and to apply this knowledge clinically. Stem cell therapies will be utilized to cure both genetic and acquired diseases and to perform successful gene therapy using the stem cell as the target for gene transfection and life-long expression of normal genes. This effort capitalizes on a critical new opportunity to develop approaches to prevent and cure a wide variety of diseases.

Decreasing Complications of Marrow Transplantation

Although bone marrow transplantation is a well-established treatment for malignant blood diseases that would otherwise prove fatal (e.g., leukemia), its use in nonmalignant blood diseases (e.g., sickle cell anemia and thalassemia) is controversial. Because the latter diseases have high morbidity but low mortality, especially in children, there is a reluctance to expose patients to the risk of treatment-related mortality from graft failure and toxic effects of the conditioning regimen used to "make room" for the new marrow. Studies in mice of a new treatment regimen in which low-dose radiation coupled with anti-host T cell antibodies are used to "make room" for the transplanted cells without destroying the original marrow have shown that recipient cells regrow along with the donor cells, resulting in the peaceful coexistence of both donor and recipient blood cells. This tolerant state is called mixed chimerism. Research in the next few years will increase our understanding of the role of mixed chimerism and speed the clinical application of marrow transplantation to treatment of nonmalignant blood diseases and, possibly, of autoimmune disorders.

T Cell Depletion in Unrelated Donor Marrow Transplantation

Within the first 3 months after bone marrow transplantation, mature donor T cells present in the transplanted marrow often react against the recipient's tissue antigens and cause severe skin rash, liver dysfunction, and diarrhea. This condition, known as graft-versus-host disease (GVHD), is such a frequent and severe complication of unrelated-donor marrow transplantation that it potentially limits the usefulness of the transplants. Approximately 49 percent of unrelated-donor transplant patients experience life-threatening GVHD. Retrospective data from the National Marrow Donor Program showed that GVHD was decreased and survival apparently improved among patients who received T cell depleted transplants. Unfortunately, T cell depletion was not risk-free; graft failure was increased. NHLBI is conducting a randomized multicenter clinical trial to determine if a reduction in GVHD by T cell depletion can be achieved without a counterbalancing increase in graft failure and relapse of leukemia in patients receiving an unrelated-donor marrow transplant. Economic analysis and quality of life assessment are part of the trial. Resolution of this important issue is expected to lead to improvements in the safety and efficacy of bone marrow transplantation.

Mutation in Factor V: A Risk Factor for Venous Thromboembolism

Thrombosis--formation of clots in blood vessels--is a major health problem that results in significant suffering and substantial economic costs. It is critically involved in the precipitation of heart attack, stroke, pulmonary embolism, and such systemic conditions as deep vein thrombosis. Women and certain other patient groups are known to be prone to thrombosis. Development of preventive measures has been hindered by lack of understanding of a clear molecular defect or risk factor. Exciting progress has now been made through research on the protein C anticoagulant pathway, an important mechanism to shut off blood clotting. Activated protein C (APC) selectively degrades two proteins, factor Va and factor VIIIa, that promote blood coagulation. Recently, NHLBI-supported investigators showed that a genetic abnormality causes a mutation in the factor V molecule that renders it resistant to degradation by APC. Because the mutation in the factor V molecule appears to be specific, and a simple test for it has been developed, opportunities now exist for prevention and treatment of a common, life-threatening condition.

Hydroxyurea Therapy for Sickle Cell Disease

The Institute just completed a clinical trial of the drug hydroxyurea, the first therapeutic agent for patients with sickle cell disease (SCD) to show promise of clinical efficacy without life-threatening toxicity. Hydroxyurea increases fetal hemoglobin, which is believed to reduce the frequency of "crises," the painful episodes that are the most common and disabling feature of SCD. The trial was halted ahead of schedule when interim analysis of data indicates that daily administration of hydroxyurea reduced the rate of crises by more than 50 percent. In addition, hydroxyurea therapy resulted in a significant decrease in acute chest syndrome, a life-threatening complication of SCD. Hydroxyurea therapy also greatly reduced the need for transfusions, which will have important public health implications for treatment of patients with SCD.

Sleep Disorders

National Center on Sleep Disorders Research (NCSDR)

The NCSDR is now fully operational. During fiscal year 1994, its first grant program made seven awards for the multicenter collaborative study "Cardiovascular Consequences of Sleep Apnea." Six clinical centers and one data coordinating center are developing a common protocol and expect recruitment to begin by the fall of 1995. The NCSDR also led the effort to develop and release a NIH-wide program announcement "Basic and Clinical Research on Sleep and Wakefulness."

The NCSDR is working closely with the NHLBI Office of Prevention, Education, and Control to develop a sleep education program. The Institute conducted a successful sleep education strategy development workshop aimed at identifying important public, professional, and patient messages for sleep. A summary of the workshop will be published in 1995. The first full education activity was a collaborative project with the National Institute of Child Health and Human Development and the Public Health Service entitled "Back to Sleep." Its purpose was to educate the public about placing babies in a supine position at bedtime to reduce risk of sudden infant death syndrome. The NHLBI has also developed several Healthbeat radio scripts for broadcast in 1995 on the importance of good sleep to health and on sleep apnea. Another series of scripts is being developed on insomnia, the relationship between sleep apnea and hypertension, and the dangers of driving while sleepy. The NCSDR is in the process of developing materials to increase public awareness of sleep and health, including a sleep apnea and insomnia fact sheet, sleep disorders data sheet, and sleep IQ quiz. Focus groups will be convened in early 1995 to assess public and patient knowledge about sleep and sleep disorders. Current plans include developing professional and patient education materials.

Smoking and Sleep Disturbances

A recent study in 3,500 adults found that persons who smoked were more likely than nonsmokers to suffer from a variety of sleep disturbances, including difficulty falling asleep, difficulty waking up, and excessive daytime sleepiness. Women smokers reported more daytime sleepiness, and men smokers, more nightmares. These results suggest that the effects of smoking, including the stimulant effects of nicotine, nightly nicotine withdrawal, and breathing difficulties associated with smoking, may increase the risk of sleep disturbances in smokers. Moreover, it is speculated that the effects of smoking on sleep could set up a vicious circle in which the symptoms of sleep disturbances (e.g., depression, fatigue, nonrestorative sleep, and impaired ability to think), by virtue of their resemblance to the effects of nicotine withdrawal, motivate the smoker to continue smoking or the ex-smoker to relapse. These results have important clinical and public health implications for reducing the disease and disability associated with sleep disturbances and smoking. They highlight the need for clinicians to assess smoking status and include smoking cessation in their consideration of treatment for sleep-related health problems.

Sleep and Hypertension

It is now recognized that sleep apnea is a highly prevalent condition in adults: severe apnea occurs in 10 percent of men and 3 percent of women. Evidence is also mounting that sleep apnea patients may have alterations in cardiovascular control that predispose to cardiovascular illness and even sudden death. New findings from a population-based sample indicate that asymptomatic sleep-disordered breathing, ranging from mild to moderate severity, is an independent risk factor for elevated blood pressure during both wakefulness and sleep. These results confirm earlier reports that the normal decline in blood pressure during sleep is diminished in persons with severe sleep apnea, and indicate that this phenomenon also occurs during much less severe episodes of apnea. Not only does blood pressure increase immediately following the apnea, but transient arousal and oxygen deficiency enhance the magnitude of the blood pressure response. This research is providing new insights into the autonomic control of pressor responses and the sustained hypertension associated with sleep apnea.

National Heart, Lung, and Blood Institute

INTRAMURAL RESEARCH

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
396	$ 98,583,000	402	$96,873,000	402	$100,737,000	--	+$3,864,000

The Intramural Research Program of the Institute conducts an exciting and diverse basic and clinical research program on diseases of the heart, blood vessels, lung, and blood in facilities at the National Institutes of Health. The Institute continues cutting edge research that has resulted in significant advances in gene therapy and bone marrow transplantation, and treatment of hemoglobin disorders. Orientation of the research program is moving toward macromolecular structure, cellular biology, molecular biology, genetics, and molecular medicine, including gene therapy. Noteworthy advances and our future plans are described in the material that follows.

Funding for this program during the last five years has been as follows:

	Amount	FTEs
FY 1991	$ 88,091,000	429
FY 1992	91,295,000	445
FY 1993	92,948,000	433
FY 1994	98,583,000	396
FY 1995	96,873,000	402

Rationale for the Budget Request

The FY 1996 budget request for the Intramural Research Program is $100,737,000, an increase of $3,864,000 over the FY 1995 level of $96,873,000.

NHLBI Bone Marrow Transplantation Unit

The NHLBI Bone Marrow Transplantation Unit (BMTU) has been operational since 1993. To date, 22 patients have received bone marrow transplants from related donors. The number of transplants has now increased to three or four per month, close to the operational maximum for this four-bed unit.

The central focus of BMTU research is the clinical problem of allogeneic bone marrow transplantation for leukemias and related disorders. The current experimental protocol evaluates a new procedure of T-lymphocyte depleted marrow transplantation followed by delayed add-back of donor lymphocytes. The goal of this approach is to prevent harmful graft-versus-host reactions while conferring significant donor immune response to the patients' residual leukemia. As a consequence, outcome following marrow transplantation should be less complicated by early mortality and late leukemic relapse. Preliminary results are favorable.

Gene Therapy to Treat Elevated Blood Cholesterol and Triglycerides

A new program has been initiated to use gene therapy in the treatment of patients who have early heart disease and high blood levels of cholesterol and triglycerides. During the past year, gene therapy was used successfully to correct such lipid defects in laboratory animals developed by genetic recombination. Defects in hepatic lipase--a major enzyme involved in fat metabolism--and apolipoprotein E--a key member of a family of proteins that helps the body direct the transport and metabolism of fats--were completely cured by using adenovirus vectors to replace the defective genes with intact ones. If these studies can be successfully extended to humans, correction of the gene defects may prevent the clinical sequelae of these lipid disorders, including early heart disease.

Advances in Antioxidants

Intramural scientists recently discovered an antioxidant enzyme that can remove the deleterious oxygen compound hydrogen peroxide, a highly reactive form of oxygen that develops during normal respiration and after exposure to light, radiation, and certain drugs. Such compounds are thought to be involved in such diverse pathological processes as atherosclerosis, cataract formation, chronic inflammation, neurological disorders, and even the aging process. The newly discovered enzyme has been found to be widely distributed in nature, and four different subtypes have been identified in humans. These observations suggest that the enzyme may have several roles. Future work will include generation of transgenic animals to study the physiological significance of the different forms of this enzyme. Elucidation of the ways in which cells normally remove deleterious oxygen compounds may lead to preventive and therapeutic procedures for the many pathological conditions that involve them.

Developments in Molecular Nutrition

The trace element selenium, which is essential in the human diet, has been found to be a key component of certain essential enzymes that control development and protect tissues from reactive organic peroxides. Scientists have discovered that selenium exists in the form of selenocysteine, a naturally occurring amino acid. Recently, it was determined that a second required trace metal, molybdenum, is also involved in several of the selenium-containing enzymes. These important enzymes are present throughout all living organisms. While exploring the synthesis of selenocysteine in bacteria, researchers found that another compound, selenophosphate, is the key biochemical intermediate in the synthesis of selenocysteine in proteins. Studies are currently under way to determine whether selenophosphate is also the selenium donor in mammalian cells and to investigate the mechanism by which this compound is synthesized. These studies are improving understanding of the role of these nutrients in normal growth, as well as their function in the body's natural prevention of disease.

Advance in Understanding How Viruses Penetrate Cells

NHLBI scientists have developed a structural model for the changes in a protein on the surface of the influenza virus that enable the virus to infect host cells. Hemagglutinin (HA), a protein in the viral membrane, is responsible for the first step in the infection process, the binding of influenza virus to the surface protein of target cells. The next step, fusion of the virus membrane with the cell membrane, is triggered by a change in the shape of HA in the acidic environment of the cellular structure into which the virus is pulled. Detailed studies of the structural changes in HA have led to a model of the shape that HA adopts to allow the viral and cellular membranes to fuse. These molecular details could point the way to the specific, deliberate design of molecules, or "designer drugs," to prevent infection.

Progress in Gene Therapy for Restenosis

Restenosis--renarrowing of the blood vessel--represents a posttreatment setback for a large fraction of patients who undergo balloon angioplasty. Research in rats showed that gene therapy can block restenosis after angioplasty-induced injury. The technique used an adenovirus carrying a gene for a herpes virus enzyme that, when expressed in cells, rendered them susceptible to the cytotoxic drug ganciclovir. These experiments will now be extended to test potential gene therapies for restenosis in pig coronary arteries, which more closely resemble human arteries. Ultimately, this approach may lead to effective gene therapy to reduce the likelihood of restenosis in patients following either coronary or peripheral angioplasty.

Angiogenesis

Progressive obstruction of coronary arteries by atherosclerosis may be counterbalanced to some extent by the natural development of collateral vessels through the process of angiogenesis. Usually, however, native collateral growth is insufficient to abolish symptoms. A growth factor protein, basic fibroblast growth factor (bFGF), administered to dogs with one coronary artery experimentally blocked, increased collateral blood flow by more than 40 percent. Studies in CHD patients to determine the safety and efficacy of bFGF in stimulating development of collateral vessels are in the planning phase. This approach has potential for improving the quality and length of life of patients with tissue ischemia due to atherosclerosis without the need for expensive bypass surgery or angioplasty.

Cardiovascular Benefits of Postmenopausal Estrogen Replacement

NHLBI scientists have observed that estrogen can produce blood vessel relaxation and expansion and significantly inhibit oxidation of LDL--low-density lipoprotein, the harmful form of cholesterol. These two observations may shed some light on the reasons why hormone replacement in postmenopausal women is associated with reduced cardiovascular events. Scientists delivered estrogen at levels normally found in premenopausal women into the hearts or forearms of postmenopausal women. It caused vasodilation by enhancing the relaxant effect of the cells that line the blood vessels--endothelium--on the underlying smooth muscles. Investigators also found that estradiol, a potent form of estrogen, inhibited LDL oxidation in postmenopausal women. Oxidatively modified LDL is believed to be important in development of atherosclerosis. Preliminary studies suggest that estrogen increases the release of nitric oxide from the endothelium and that nitric oxide protects LDL from oxidation. Other vascular effects of estrogen therapy are also being investigated. An understanding of estrogen's vascular effects may lead to development of alternative therapies to prevent or retard atherosclerosis in a way that reduces adverse effects in women, and may prove useful in men as well.

Hypertrophic Cardiomyopathy

NHLBI scientists have demonstrated that chronic pacing of the left ventricle (LV) of patients with hypertrophic cardiomyopathy (HCM) relieves LV obstruction and severe symptoms that do not respond to drugs. HCM, the most commonly inherited heart disease in the United States, often results in obstruction of LV outflow. In most HCM patients, installation of a cardiac pacemaker can now replace the much more difficult cardiac surgery that has been conventional therapy. These studies are now being extended to determine if cardiac pacing can prevent development of LV obstruction and hypertrophy in HCM children during the period of greatest growth. Other ongoing studies promise to shed light on mechanisms of sudden death in athletes who have and determine whether it is possible to identify a low-risk group of athletes who may be allowed to participate in competitive sports.

National Heart, Lung, and Blood Institute

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
456	$56,630,000	455	$57,994,000	445	$59,745,000	-10	+$1,751,000

The Research Management and Support budget activity provides funds for the overall management of the Institute's programs; for the education programs in the Office of Prevention, Education, and Control; and for international cooperative research activities. One of the most important uses for these funds relates to the coordination of activities that cut across program lines such as the National Center on Sleep Disorders Research, minority health and training, women's health issues, AIDS research, international cooperative research agreements, and administrative initiatives, for example, new agreements with the private sector authorized by the Federal Technology Transfer Act.

Funding for this program during the last five years has been as follows:

	Amount	FTEs
FY 1991	$51,596,000	469
FY 1992	56,880,000	484
FY 1993	56,719,000	476
FY 1994	56,630,000	456
FY 1995	57,994,000	455

Rationale for the Budget Request

The FY 1996 budget request for Research Management and Support is $59,745,000, an increase $1,751,000 over the FY 1995 level of $57,994,000.

National Center on Sleep Disorders Research (NCSDR)

The NCSDR was established in June 1993, as part of the 1994 NIH Revitalization Act, to support research, conduct health education activities, and coordinate sleep and sleep-related research within the NIH and across the Federal government. The Sleep Research Advisory Board has been appointed and held its first meeting in August of 1994. Dr. Thomas Roth, who heads the Sleep Disorders Research Center at the Henry ford Hospital in Detroit, Michigan, was elected chairperson. The Board established research and education subcommittees to carry out its primary functions. The research subcommittee is currently working on the sleep research plan for the Director, NIH, and the education subcommittee is providing input on sleep education messages. The Board meets twice a year, and the next meeting is scheduled for March of 1995.

The NCSDR is also responsible for the Trans-NIH Sleep Research Coordinating Committee. The Committee meets every other month to discuss activities in various NIH sleep-related programs. The Committee is planning a workshop for the fall of 1995 on "Cellular and Molecular Mechanisms of Circadian Rhythm and Sleep Control" and developing a research training program announcement for possible release in late 1995.

The NCSDR is working with other government agencies on sleep-related activities. It cosponsored a national forum on sleepiness and traffic safety with the Department of Transportation and the National Sleep Foundation. The NCSDR continues to collaborate with the National Aeronautics and Space Administration on the neurolaboratory project.

Administrative Reforms

The Institute has sought and continues to seek new and different ways to manage its programs and implement the recommendations contained in the National Performance Review. NHLBI's BOLD Committee, made up of senior Institute staff, submitted a final report in June 1994 that has led to a streamlined organizational structure and more efficient program operations. The new organizational structure, which eliminated 42 formal Offices/Branches/Sections and consolidated functions, has enabled the Institute to reduce its FTE requirements, change its supervisor-to-employee ratio from 1:4 to 1:13, and reduce the number of senior level staff required to carry out program activities.

To facilitate and support these significant changes in structure and staff responsibilities, the Institute initiated two major human resource initiatives. The first is designed to develop a series of mid-level professional positions to accommodate a transfer of technical duties from senior level science administrators to offset the reduction in GS-14 and GS-15 staff. This new career track initiative also assists in the upward mobility of talented staff at lower grade levels, particularly minorities. The second initiative implements a comprehensive Human Resource Management (HRM) framework by establishing guiding principles for HRM within NHLBI that include employee participation at all levels within the organization.

The Divisions that manage the extramural research programs of the Institute are moving to a single off-campus facility in March 1995 from two separate off-campus sites. This relocation provides a unique opportunity to accommodate the changes created by the new organizational structure implemented October 1, 1994.

Education Programs

The Office of Prevention, Education, and Control (OPEC) reorganized into a project team management structure during FY 1994. This structure will encourage greater efficiencies in operating the national programs and at the same time create a new capacity to rapidly respond to advances in medical and public health sciences. OPEC anticipates increased interest in its products and services and has positioned itself to assure timely dissemination of prevention research results.

Increasing Diversity

The Institute has increased significantly its efforts to diversify its employment profile and augment the number of scientists from underrepresented groups in its intramural and extramural research programs. Based on data that showed a need to increase the numbers of minorities enrolled in the sciences, programs have been expanded to include primary, secondary, and undergraduate students. These new approaches will help the Institute achieve a diverse and balanced staff reflective of the Nation's work force.

The Institute continues to assess current policies and procedures to ensure that affirmative action initiatives are effective. For example, the working groups formed to help implement our HRM framework are evaluating the way in which we recruit, select, and supervise staff and provide for their career development so that we continue to increase diversity while being fair to all groups.

Looking to the future, the Institute is reaching out to minority groups and institutions to increase interest in research careers in the biomedical sciences in general, and heart, lung, and blood diseases in particular. The following table displays targeted student population groups and the programs designed to reach each group.

NHLBI Continuum for Increasing Diversity Among Scientists

Key:
HBCU: Historically Black Colleges and Universities
NRSA: National Research Service Award
IRTA: Intramural Research Training Award
NIH: National Institutes of Health
NHLBI: National Heart, Lung , and Blood Institute
BOLD: New in FY1994 or FY1995

Elementary/ Junior

- Adopt-A-School
- ***PC Loan/Donation***
- Intern/Partnership Program
- Research Supplements for Disabled or Minority Students

Senior High

- Stay-in-School
- NIH Summer Program
- Research Supplements for Disabled or Minority Students
- Intern/Partnership Program

Under Graduate

- ***NHLBI Minority Biomedical Research Training Program***
- Minority Access to Research Careers (MARC)
- NIH Summer Internship Program
- Native American Intern Program
- NRSA (short term training)
- Research Supplements for Disabled or Minority Students

Graduate

- ***NHLBI Minority Biomedical Research Training Program***
- Post College IRTA
- PRE-Doctoral IRTA
- NIH Summer Research Fellowship Program
- NIH Summer Internship Program
- NRSA
- Research Supplements for Disabled or Minority Students

Post-Graduate

- IRTA
- Tenure Track
- Staff Fellows
- ***Epidemiology & Biostatistics Training Program***
- ***Clinical Training Fellowship Program***
- NIH Summer Internship Program
- NRSA
- ***Science Education Program for HBCUs***
- ***Research Development Award for Minority Faculty***
- Minority School Faculty Development Award
- Clinical Investigator Development Award
- Research Career Development Award
- Research Supplements for Disabled or Minority Students

National Heart, Lung, and Blood Institute

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	10	10	10
Office of Program Planning and Evaluation	33	33	32
Office of International Programs	8	7	6
Office of Prevention, Education and Control	34	34	33
Office of Administrative Management	50	50	49
Division of Heart and Vascular Diseases	68	68	67
Division of Epidemiology and Clinical Applications	78	78	76
Division of Lung Diseases	31	31	30
Division of Blood Diseases and Resources	31	31	30
Division of Intramural Research	396	402	402
Division of Extramural Affairs	112	111	109
National Center on Sleep Disorders Research	1	2	3
Total, NHLBI	852	857	847

Average GS/GM Grade

1990	10.00
1991	10.04
1992	10.05
1993	10.03
1994	10.46
1995	10.42
1996	10.30

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive Level I	0	0	0
Executive Level II	0	0	0
Executive Level III	0	0	0
Executive Level IV	0	0	0
Executive Level V	0	0	0
Subtotal	0	0	0
Total-Exec Level Salaries			
ES-6	3	3	3
ES-5	2	2	2
ES-4	11	11	11
ES-3	0	0	0
ES-2	0	0	0
ES-1	3	3	3
Subtotal	19	19	19
Total - ES Salary	$2,078,410	$2,115,000	$2,147,000
GS/GM-15	68	67	66
GS/GM-14	80	79	78
GS/GM-13	65	65	64
GS-12	58	60	58
GS-11	81	82	79
GS-10	9	9	9
GS-9	49	50	50
GS-8	42	42	42
GS-7	107	110	110
GS-6	31	31	31
GS-5	23	25	23
GS-4	3	3	3
GS-3	2	2	2
GS-2	1	1	1
GS-1	2	2	2
Subtotal	621	628	618

	1994 Actual	1995 Estimate	1996 Request
Grades established by Act of July 1, 1994 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	27	27	26
Senior Grade	16	16	16
Full Grade	16	16	16
Senior Assistant Grade	4	4	4
Assistant Grade	0	0	0
Subtotal	64	64	63
Ungraded	145	151	141
Total positions, end of year	849	862	841
Total FTE, end of year	852	857	847
Average ES level	4	4	4
Average ES salary	$109,390	$111,345	$113,030
Average GS/GM grade	10.46	10.42	10.30
Average GS/GM salary	$44,575	$45,774	$45,840

WEDNESDAY, MARCH 15, 1995.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. DUSHANKA V. KLEINMAN, ACTING DIRECTOR AND DEPUTY DIRECTOR

DR. HENNING BIRKEDAL-HANSEN, DIRECTOR, DIVISION OF INTRAMURAL RESEARCH

DR. L. JACKSON BROWN, DIRECTOR, DIVISION OF EPIDEMIOLOGY AND ORAL DISEASE PREVENTION

DR. LOIS K. COHEN, DIRECTOR, DIVISION OF EXTRAMURAL RESEARCH

EARLENE S. TAYLOR, BUDGET OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. BONILLA [presiding]. The committee would be pleased to hear at this time from Dr. Kleinman, National Institute of Dental Research.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Allow me to introduce, sitting behind me, the Director Designate of the National Institute of Dental Research, Dr. Harold Slavkin, who's a distinguished professor, cell biologist, center director, and dentist from the University of Southern California who will be joining the NIH this year.

Mr. BONILLA. Welcome. We're excited you're here and look forward to working with you, Doctor.

Dr. KLEINMAN. Now that we're settled, thank you very much.

You know Dr. Varmus and Mr. Beldon. To my right is Ms. Earlene Taylor, our Budget Officer. And to my left are three division directors, Dr. Lois Cohen, the Director of the Division of Extramural Research; Dr. Henning Birkedal-Hansen, our Director of the Division of Intramural Research; and Dr. Jack Brown, the Director of the Division of Epidemiology and Oral Disease Prevention.

We have been working as a team during this year of transition. We have benefitted from the momentum of programs that Dr. Harald Loë put in place, who retired last May. Now we're looking forward to the leadership of Dr. Harold Slavkin, who will arrive in July.

OPENING STATEMENT

This committee, Mr. Chairman, has been saving and is saving the people of the United States $4 billion a year. This is an estimate of actual dental expenditure savings that have resulted from fewer teeth being pulled, fewer dentures being made, and fewer crowns and bridges being placed. Over the years, this committee's investment in basic dental research at NIDR has led to a greater understanding of the causes of oral diseases and how to prevent them.

The translation of these scientific findings into clinical practice has basically revolutionized the face of dentistry and has dramatically improved the oral health of the Nation. We are now looking forward to further savings.

The mouth is a mirror of health and disease. Often, the first signs of disease or of a dietary deficiency are seen in the mouth. The unique focus of the research at NIDR is on the extraordinary tissues of the teeth, the mouth, the face, and the jaws. Just as the mouth is a mirror of the body, the research we support has benefitted all body organs and systems.

I just returned from the 24th annual meeting of the American Association for Dental Research in San Antonio, Texas, where over 5,000 research scientists presented their latest findings. I'll deviate from my prepared statement a little to give you an update of the exciting discoveries and give you an example of the breadth and scope of dental research.

First, designer teeth and designer bones are just around the corner. Basic research is teaching us about the wonders of molecular factors involved in hard tissue growth. Bone, connective tissue, dental and periodontal diseases affect all of us. Scientists reported the discovery that several molecules isolated from bone or dentin tissue stimulate new bone and tooth growth in animal models. Imagine a therapy using bone morphogenetic proteins that could eliminate the need for root canal therapy.

In another study, cells taken from patients' own bone marrow developed into bone-forming cells in animal models. With further testing, this novel technique will be used to generate new bone in the jaws of patients who have lost all their teeth. A clinical therapy to augment bone and cartilage formation will be extremely important when considering osteoporosis, and hip, limb, and jaw fractures.

Second, saliva provides significant promise for prevention and for the diagnosis of many systemic diseases. Saliva allows us to speak and to swallow. It is key to the prevention of dental caries. It's a readily accessible fluid already being used to diagnose hormone levels, medication use, and drug levels. And it protects from infections and invasions by a multitude of microorganisms. I don't know about your grandmother, but my grandmother used to say, "Lick your wounds if you're hurt on the playground and can't get to some water."

Well, our latest discovery is a protein found in saliva that inhibits the AIDS virus from invading cells in the immune system. The protein is SLPI, Secretory Leukocyte Protease Inhibitor, which appears to function on the cell membrane, not on the virus itself. We're moving ahead with this very promising research because we propose to use SLPI as a possible HIV therapy.

I wish to add that this research was based on the observation that oral transmission of AIDS is relatively rare, and that something in the mouth—saliva—is protective.

Third, structural and molecular investigations of pain are making significant progress. Using new imaging techniques, NIDR scientists are learning what structures of the brain are affected by pain. Expanded understanding of the complex pathways of pain is leading to improved pain management. Pain disorders where nerves are damaged, the neuropathies, are some of the most intractable. Recently, NIDR investigators found that neuropathic pain is mediated in part by a molecule called the NMDA receptor.

We now have some medications that can block this receptor, but they have quite extensive side effects. In new studies, our scientists discovered that commonplace drugs, like a cough suppressant, or medications used to treat Parkinson's disease, may be effective and can block this receptor with limited side effects. Safer, more specifically targeted drugs can be found, and combinations of drugs may be the answer that our pain patients so badly need.

Fourth, the unique properties of the oral tissues and glands for gene therapy and gene therapeutics are rapidly emerging. Salivary glands of rats have been altered to produce a protein, histatin, which effectively fights yeast infections. With further development, you can imagine that the salivary glands of immunosuppressed patients could be converted into factories literally producing histatin to prevent yeast infections, as well as to prevent other infections. Just last week, we learned that the tongue muscle, and only the tongue, not cardiac muscle or limb muscle, can be used for gene therapeutics for systemic diseases.

In another case, NIDR scientists have genetically engineered skin cells in animals to produce a secretory protein, which is key to the regulation of cholesterol metabolism.

Well, as you've heard already yesterday and today and will hear in the coming days, basic research is the engine that drives clinical progress to improve the general health of the American people. And as we advance in the 1990s, the NIDR continues to support research to reduce the societal burden from hundreds of diseases like oral cancer, dental caries, periodontal diseases, and cleft lip and cleft palate. The rapid development of our understanding of molecular and behavioral events on growth and development, on health and disease, are positioning us to address challenges with precision as never before.

The estimate of $4 billion a year in actual dental expenditure savings is one and a half times the cumulative appropriations to this Institute over the past 47 years. Your investment in basic biomedical research clearly has had profound effects for the economy as well as for the health of the Nation. Science for the prevention of disease and for the promotion of health remains our goal.

Mr. Chairman, the fiscal year 1996 budget request for the National Institute of Dental Research is $168,341,000. I'd be happy to answer any questions.

[The prepared statement and biography of Dr. Dushanka Kleinman follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Dental Research

The unique focus of research of the National Institute of Dental Research are the tissues in and around the mouth and the hundreds of conditions that can affect them. Among the most common are infectious disorders like tooth decay--still the most prevalent disease in children. Other problems are due to congenital defects, trauma, medications, and autoimmune disorders.

Just as the mouth is the gateway to the body, the research we support has been a gateway to understanding other body organs and systems. Studies of craniofacial bones and muscles have advanced our knowledge of skeletal bone and disease; studies of the jaw joints--the most complex joints in the body--not only illustrate the wonders of nature's engineering, but are helping us understand other joint problems. Tooth development studies are providing a model for the study of gene expression and cell communication. The extraordinary sensitivity and mobility of the mouth have inspired neuroscience research--especially effective in advancing understanding of pain and its control. Finally, the position of the mouth--literally open to environmental insult and injury--is leading to new findings on how the mouth defends itself and guards the body from harm.

Pain is a $100 billion problem in America. The management of pain had its genesis in dentistry with the introduction of nitrous oxide and ether in the 19th century. As many of us know from personal experience or from our friends or relatives, the toll taken by headache, jaw disorders, arthritis, osteoporosis, low back pain, cancer and cancer treatment is immeasurable. Disorders such as reflex sympathetic dystrophy, in which there is nerve damage (neuropathy) associated with a severe and diffuse burning pain, are among the most intractable. Recently our investigators have found that neuropathic pain is mediated in part by a molecule called the N-methyl-D-aspartate (NMDA) receptor. While a number of drugs can block the receptor, their use is limited by side effects. In new studies our scientists discovered that a widely used cough suppressant, dextromethorphan, can block the NMDA receptor. The drug memantine, used to treat Parkinson's disease, has also proven effective in animal studies. Thus we believe that safer, more specifically targeted NMDA receptor blockers can be found and, when combined with pain medications that work by other mechanisms, could provide the kind of enhanced and sustained pain relief neuropathy patients need.

We are also moving ahead in studies of jaw (temporomandibular) disorders or "TMDs," which have become a source of unremitting pain and dysfunction for a large and predominantly female population. The problem is compounded in individuals who have had surgery to replace parts of the joint with plastic prostheses. NIDR has pursued research to clarify the diagnoses of TMDs, and is supporting studies of preventive and conservative treatments. With the collaboration of other NIH components, we sponsored the first International Workshop on TMDs and Related Pain Conditions in 1994,laying the groundwork for research that can be pursued immediately. Especially emphasized were the need to study the interactions of the nervous, endocrine and immune systems in response to tissue injury; develop animal models; and increase molecular biology studies of the mechanisms underlying deep muscle and joint pain.

No less important that chronic pain problems are the bone and connective tissue diseases that affect millions of Americans, including the hereditary disorders and bone cancers that occur early in life; periodontal diseases in maturity; and the crippling conditions of osteoporosis, Paget's disease, and arthritis that beset growing numbers of adults and elderly. With a rich background of study of the hard tissues of the mouth, our scientists are acknowledged world leaders in basic bone biology. Now they have taken the lead in establishing a new Bone Clinic in the NIH Clinical Center, to move basic research into the clinical arena. The first protocol typifies the interplay between oral and general health: The investigators have isolated primordial "stem" cells from human skeletal bone marrow and found that these cells can develop into bone-forming cells in animal models. With further confirmation of these findings, the NIDR team will use this technique to generate new bone in the jaws of patients who are missing all their teeth. The same approach can be used to fill other bony defects in the body.

In the course of studying how the mouth protects the body from infection, oral health scientists are making pivotal discoveries about the body's immune system, especially the system of "secretory immunity" involving the cells that form the mucosal linings of the mouth and other organs. In addition, they are documenting the special role of saliva: An increasing number of salivary components have been discovered with broad antibacterial and anti-fungal properties. Most recently, our scientists have evidence that saliva contains a factor that inhibits infection by HIV--the AIDS virus. Since 1981, when the epidemic was first recorded, there have been few cases of oral transmission of AIDS. The scientists suspect the reason for this is a protein in saliva called Secretory Leukocyte Protease Inhibitor (SLPI). When they exposed immune cells to small amounts of SLPI in a test-tube and then added HIV, the virus was not able to invade the cells. Even when they washed SLPI out of the test-tube and added fresh HIV, the cells remained uninfected for up to three weeks. They surmise that SLPI may act by coating the immune cells in some way rather than attacking HIV directly. More research is obviously called for, with the potential for the development of a promising new AIDS drug.

Vigilance against infection is the hallmark of oral defense mechanisms. If salivary production is undermined, if oral hygiene is poor, if diet is inadequate, the balance may tip from health to disease. We know that certain diseases like Sjögren's syndrome, in which the salivary and tear glands are destroyed, can lead to rampant tooth decay, as can radiation to the head and neck or drug treatment for cancer. We know that diabetes patients are at increased risk for periodontal diseases, and that oral symptoms are often the first signs of HIV infection. Children born with cleft lip or palate or with genetic diseases that affect the craniofacialand oral tissues have special problems that may lead to painful, costly and multiple surgeries and rehabilitation services over the lifetime.

Recognition of these problems has led NIDR to increase basic research on the diseases in question. This includes the support of centers studying the genetic and environmental causes of craniofacial birth defects and expanded research in molecular epidemiology, in which investigators study families with hereditary craniofacial disease, or try to determine the risk factors for a disease like oral cancer in selected populations. We are also conducting clinical studies and trials on how best to prevent periodontal diseases in diabetic patients, and we have begun a clinical trial to determine if rigorous preventive approaches can forestall oral complications in HIV patients.

Another major initiative has as its focus the oral health of the nation's ethnic and racial minorities. We know that African-Americans and Hispanics are at heightened risk for diseases like diabetes, and our surveys tell us that oral health is generally poorer among minorities. These findings led the Institute to initiate six planning grants for Regional Centers for Minority Oral Health three years ago. The results have been promising and the schools are now competing for full-scale five-year awards to be made later this year.

To serve the public and the many patients with "special care" problems, the NIDR provides in-house information services and in 1994 established a National Oral Health Information Clearinghouse. "NOHIC" maintains the only database of oral health and disease materials specifically targeted to the public and care providers. By year's end the Institute and the Clearinghouse had responded to some 30,000 requests by phone, mail, fax or Internet.

The NIDR mission is to improve the oral health of the American people. Our research has enabled us to travel far along that road, and with the use of the oral tissues as models of health or disease elsewhere in the body, is enhancing general health as well. Importantly, the new and expanded preventive measures we have pioneered have changed dental practice and home care, reduced the cost of dental services, and contributed to an estimated savings in the nation's dental expenditures on the order of $4 billion a year. That trajectory toward prevention began even earlier, however, with an unprecedented experiment in public health pioneered by the scientists who became the first Directors of NIDR: Fifty years ago this January, Grand Rapids, Michigan became the first city in the world to fluoridate its water supply--an event we can justly celebrate as a turning point in the history of dentistry and dental science.

Mr Chairman, the FY 1996 budget request for the National Institute of Dental Research is $168,341,000. I will be happy to answer any questions.

DUSHANKA V. KLEINMAN, M.Sc.D., D.D.S

Current Position: Acting Director and Deputy Director, National Institute of Dental Research

Birthplace and Date: Podkoren, Yugoslavia, August 18, 1948

Citizenship: USA

Education: B.S., University of Wisconsin, 1969; D.D.S., University of Illinois, 1973; Internship, Zoller Dental Clinic, University of Chicago, 1974; Dental Public Health Residency, Boston University, 1976; M.Sc.D., Boston University, 1976.

Professional History: 1966-69, Laboratory Research Assistant, University of Chicago; 1970, Dental Claims Auditor, California Dental Service; 1971-72, Dental Assistant, Lakeside Dental Clinic, Chicago; 1973-74, Dental Intern, Zoller Dental Clinic, Chicago; 1974-76, General practice, Brookline Health Department, Brookline, Mass., and Boston University; 1976-78, Assistant Professor, Baltimore College of Dental Surgery, University of Maryland; 197880, Staff Dental Officer, Bureau of Health Manpower; 1980-83, Evaluation Officer, NIDR; 1983-86, Chief, Planning and Evaluation Section, Office of Planning, Evaluation and Communications, and Planning Officer, NIDR; 1986-87, Special Assistant for Program Coordination, Epidemiology and Oral Disease Prevention Program, NIDR; 1987-90, Chief, Soft Tissue, Craniofacial Defects and Pain Section, NIDR; 1990-91, Special Assistant for Program Activities, Office of the Surgeon General; 1991-present, Deputy Director, NIDR; 1994-present, Acting Director, NIDR.

Commissioned Officer, U.S. Public Health Service, 1978 to present. Current rank, Captain.

Honors, Awards: Fellow, International College of Dentists, 1993; PHS Citation, 1993; PHS Jack D. Robertson Award, 1993; Distinguished Alumni Award, Boston University, Henry M. Goldman School of Dentistry, 1993; PHS Outstanding Service Medal, 1992; PHS Surgeon General's Exemplary Service Medal; Fellow, American College of Dentists, 1988; PHS Special Citations, 1987 and 1985; PHS Outstanding Service Medal, 1986; PHS Commendation Medal, 1984; Named in "Outstanding Young Women in America", 1982; Meritorious Award, American Dental Association's Community Preventive Dentistry Award, 1977.

Professional Organizations: American Association for Dental Research, American Association of Dental Schools, American Association of Public Health Dentistry, American Association of Women Dentists, American Board of Dental Public Health, American Dental Association, American Public Health Association, Commissioned Officers Association of the U.S. Public Health Service, Federation Dentaire Internationale, International Association for Dental Research.

Editorial Boards: Journal of the American Dental Association, 1993-present; Journal of Public Health Dentistry, 1990-present; Community Dentistry and Oral Epidemiology, 1987-present.

Mr. PORTER [resuming]. Dr. Kleinman, thank you very much for your good statement. I want to also welcome you here this morning and your staff.

Dr. KLEINMAN. Thank you very much.

SAFETY OF FLUORIDATED WATER

Mr. PORTER. Your statement mentions the fact that this year is the 50th anniversary of the first city to fluoridate its water. We're familiar of course with the success story in terms of reduced cavities. In fact, I've read that the lifetime cost of fluoridating water for one person is less than the cost of a single filling.

As a result, I find it surprising that 30 percent of cities with populations of more than 100,000 people don't fluoridate their water supply, including Los Angeles and San Diego. Are there lingering concerns about the safety of fluoride that discourage these cities from fluoridating their water, or why is that so?

Dr. KLEINMAN. We have no concerns about those cities proceeding with fluoridating water. In fact, we see fluoride as a magnificent mineral. We've been monitoring it over the years, and continue active research programs.

There have been recent thorough evaluations of the health benefits and risks associated with fluoride over the past few years including the report in 1991 from the Committee to Coordinate Environmental Health and Related Programs and, most recently, from the National Academy of Sciences on the toxicology of fluoride. So we see it as a safe, effective means to prevent dental caries.

At this time, 62 percent of all cities that have community water supplies are fluoridating. For the remaining 38 percent, there are many complex issues. One is, water fluoridation requires referenda in some states. That brings in a lot of issues related not just to fluoridation and community water supplies, but other issues that affect environmental health, as well as other concerns.

Los Angeles, as an example, has three water supplies: one of which is fluoridated; another has naturallly occurring optimum levels of fluoride; and the third is unfluoridated. So you have to take a look at the means by which those cities would have to be approached to optimally raise the level of fluoride.

I want to add one thing, that fluoride is an ideal public health preventive measure, and it's given us a standard that we're trying to meet with all our other public health measures.

Mr. PORTER. Do you see differences in the places in Los Angeles served with the different supplies, or are they intermingled?

Dr. KLEINMAN. My understanding is that there are differences. However, there are several things to consider when you have a mixture of water supplies. Also, the ingestion of other liquids that populations have beyond the water supply is a confounding factor to not only what's in the water supply, but the food and the diet as well. In addition there are factors of income and poverty and education that affect disease levels as well. And I think from my understanding of Los Angeles, we're seeing all those factors come into play.

USE OF SALIVA IN AIDS TREATMENT

Mr. PORTER. You mentioned in your testimony the protein in the saliva that seems to block the AIDS virus. Obviously you're pursuing this, but how do you translate this into a treatment or prevention methodology? You mentioned it works on the cell. How do we go from where we are to where we can find this useful?

Dr. KLEINMAN. We're at a very early stage, as you know, in exploring this property of saliva. One of the considerations that we've given here is possibly using this as a barrier technique to prevent the invasion of cells by HIV. Another possible approach, and these are still very far down the road, I must emphasize, is to use it in the treatment of AIDS intravenously to inhibit the further infection of cells and allow the immune system to rebound.

Mr. PORTER. How would you use it as a barrier?

Dr. KLEINMAN. It could be as a lubricant, but probably more as a topical application.

NEW GENERATION OF PAIN KILLERS

Mr. PORTER. Dr. Kleinman, your Institute, of course, has the lead on pain research, and you operate a pain clinic at the clinical center. We read that a new generation of pain killers is coming on line, and I guess that's perhaps what you were referring to in your oral testimony. We understand that some of them will have fewer side effects that are troublesome and offer greater relief. And I think people all over are awaiting word on when these drugs will be available from their doctors. How soon will this new generation of pain killer be marketed, and are those drugs different from those currently available?

Dr. KLEINMAN. Well, we're testing, as I mentioned, existing drugs on the market that could be applied to pain management, and we're looking at new drug development as well. We're in the relatively early stages of some of these. The ones that are on the market already, obviously, are closer to being able to be used for application for pain management.

NEW BONE CLINIC AT NIH

Mr. PORTER. You've established a new bone clinic at the clinical center. What will be the major focus of this clinic in the development of bone growth factor and what protocols have been planned?

Dr. KLEINMAN. Well, we have had a long-range commitment to hard tissue research, you can imagine, starting with the teeth and moving out to the jaws, looking at their structures and then moving into the living organs themselves, the cells and the extracellular matrix. The bone clinic is a collaborative effort at NIH, including the Arthritis Institute and many other Institutes on campus. It is one that we have seen as an opportunity to move basic research findings into clinical application.

One protocol that is in place right now is focused on the example I gave in my opening statement: taking human marrow cells from the patient and having them grow into bone-forming cells in an animal model, a mouse in this case, to then be put back into the same patient's jaws to regenerate.

There's an interest in the Cancer Institute in osteosarcoma, in the Child Health Institute in osteogenesis, the Arthritis Institute in osteoarthritis, as well as in the Aging Institute, for example, in osteoporosis. It's a cross-cutting effort which we think will be exciting not only at the NIH campus, but in collaboration with the external community as well.

MINORITY RESEARCH CENTERS

Mr. PORTER. This year, you will be awarding full grants for regional minority health centers, after several years of planning grants. How many full grants do you expect to award, and what minority health areas are you hoping to emphasize?

Dr. KLEINMAN. At this point, we're envisioning about three to four regional centers in minority oral health. As you know, we have six planning grants in place that resulted from advice from the extramural community and our assessment of the status of oral health in minority populations.

Like the precursor planning grants, the formal grants will have three primary objectives. One is to pursue research that benefits minority oral health, from basic research all the way through applied research. A second is to ensure the development of minority oral health researchers through career development and training programs. The third area is to ensure the infrastructure in minority institutions and in institutions serving a large number of minority populations. And they'll be looking at the broad-based issues as well.

Mr. PORTER. Mr. Bonilla.

SEVERE CARIES IN INFANTS

Mr. BONILLA. Thank you, Mr. Chairman.

Doctor, it's my understanding that in spite of the great advances in research, especially the advances against tooth decay, that certain segments of our population are afflicted with severe caries, which you mentioned briefly in your opening remarks, specifically children. Could you tell me more about this condition and who is more likely to be stricken by caries, and has your Institute developed any kind of research agenda for this disease?

Dr. KLEINMAN. Well, as you've pointed out, tooth decay is not just one disease; it has multiple component parts. One category of dental caries is the very severe caries seen in infants and young children, as soon as they get their teeth.

Mr. BONILLA. You say the mouth is a mirror of your health, so it is easily spotted just visually?

Dr. KLEINMAN. In this particular disease that you've mentioned, it's extremely easily spotted. Now, one type of severe infant caries has been identified to be caused with baby bottle feeding habits, in which mothers have put children to bed with milk or juice. And it causes a specific pattern of tooth decay in the top teeth, and actually looks like little moon shaped cavities between the teeth themselves. It's very rapid, very severe, painful and expensive to treat.

Now, the cause of this is, caries is a bacterial disease, and the milk and the juice promote its development. Thus caries isn't only dependent on bacterial causes, but on the diet, and this is where that comes in, but also the nutritional development of that infant and infections these children may have that may predispose them more adversely than others to this disease.

Mr. BONILLA. So you say then you have a research agenda?

Dr. KLEINMAN. We have specific initiatives including those focused on severe infant caries, as we're calling it. We are looking at issues of transmission of infections from caregivers to infants, various causes of the disease, and ways to prevent it. We're focusing on it through collaborations as well, not only at NIH and within our Institute, but with the Centers for Disease Control and other agencies like the Indian Health Service, where they're directing specific health promotion programs in the community.

MINORITY RESEARCH CENTERS

Mr. BONILLA. Have any of the regional research centers on minority oral health turned any attention to the needs of Hispanic Americans?

Dr. KLEINMAN. Yes. We have, as I said, six planning grants in place. The one that is located at San Antonio at the University of Texas is primarily focused on issues of Hispanic health, especially the interaction between diabetes and periodontal disease. There are also projects in New York and in the Los Angeles area that address the health of Hispanics.

NATIONAL SURVEY OF SCHOOLCHILDREN

Mr. BONILLA. On another subject, the survey of oral health of schoolchildren. Can you explain what knowledge you hope to gain with the results of this survey?

Dr. KLEINMAN. Within the NIDR, we've conducted two national surveys of schoolchildren, taking a look at not only tooth decay but also periodontal disease and, most recently, the effects of tobacco use in adolescents on oral health, looking at mucosal lesions, and herpes infections as well as ulcers or canker sores.

We're looking to see whether the gains that we have made—when we look from 1979 to 1986–1987, we see dramatic improvements in the caries-free permanent dentition of schoolchildren. Almost 50 percent of the children were caries-free in their permanent teeth at the time of the last survey. What we're looking for at this point in time is to see whether those improvements are continuing, and we're also going to be considering the additional assessment of the molecular aspects and biomarkers of oral diseases and conditions.

Mr. BONILLA. What was the percentage before that? You said it was 50, so was it a lot different in previous years?

Dr. KLEINMAN. It's a major improvement. I was going to ask Dr. Brown to give us the specifics for it.

Dr. BROWN. It's been over a 50 percent decline since the early 1970s. At that time, the caries-free rate in permanent teeth of schoolchildren was about 26 percent. And it was around 50 percent in 1986–1987. And our more recent data indicates it will be around 55.

DESIGNER TEETH

Mr. BONILLA. I have one final question, Dr. Kleinman. You mentioned something about designer teeth in your opening remarks. What do you mean by that?

Dr. KLEINMAN. It got my curiosity, too, when I heard it in San Antonio last week. Basically those same bone morphogenetic proteins that I mentioned that can stimulate bone growth have been used in, I believe, a chimpanzee model. What they've done is they've created a cavity in the teeth, simulating a tooth that would need root canal treatment. Then they have placed the protein within the depths of the cavity, and have seen the regeneration of dentin, capping the tooth pulp. Thus it may be possible to biologically repair and restore the function of the tooth without having to incur an average of $500 for a root canal treatment first, and then second the placement of a crown on that tooth itself.

We are very excited about what the potential is.

Mr. BONILLA. It's exciting to hear about that, also because when you refer to something as designer-oriented, it sounds like somebody's developing it with a star on it or a logo or tattoo or something like that. [Laughter.]

Thank you, Dr. Kleinman.

Dr. KLEINMAN. Thank you.

NEW RESEARCH ON CRANIOFACIAL BIRTH DEFECTS

Mr. PORTER. Dr. Kleinman, I have two more questions for you, and then I have two questions for Dr. Varmus, if I may.

One of the Nobel laureates that appeared before our subcommittee two weeks ago, Dr. Joseph Murray, expressed his great personal interest in craniofacial birth defects. He said he only wished he had another 30 or 40 years in science to explore the genetics of this condition. Will it take another 30 or 40 years, and have you made any significant inroads into understanding these genetic disorders?

Dr. KLEINMAN. Well, it's an exciting field. And it's one that links us, again, to the total body of these congenital anomalies, those that affect the craniofacial area. Last year, we reported a linkage between one of the homeobox genes and one form of a syndrome called craniosynostosis. Actually, there are a hundred forms of craniosynostosis.

Just last month in *Nature Genetics* the identification of three fibroblast growth factor receptors that contribute to the premature closure of the skull bones in craniosynostosis were reported. That's five additional craniosynostosis syndromes that were identified. So at that rate, this is an exponential rate of one last year, five this year, we keep on, there will be a handful of years before we can explore this area, which is one of the congenital anomalies.

In cleft lip and cleft palate, we have moved toward the development of animal models and actually, you're speaking about the area of research that our future director, Dr. Harold Slavkin, is in. And we're looking forward to rapid development in the area of understanding these congenital anomalies through developmental biology research.

Also, we have identified about a thousand genes associated with the teeth, the jaws, and the craniofacial structures, 60 percent of which have not been previously identified. And we're making major inroads here to specify those related to the dental tissues and to collecting the cells.

MERCURY-CONTAINING AMALGAMS

Mr. PORTER. We understand that you are continuing your research into the possible alternatives to the use of mercury in amalgams. Can this sort of work be supported through cooperative efforts with the private sector? I would think this would be a natural area for industry collaboration because of the market potential of the product.

Further, your justification describes a study you're doing of Vietnam veterans with the Air Force on the effects of mercury. Can you say anything yet about the data analysis that is underway?

Dr. KLEINMAN. Well, to answer your first question, in terms of collaboration with industry in the development of a mercury-free amalgam and other restorative materials, we are and have been working closely with industry and have partnerships not only through collaborative research and development agreements, but with the National Institute of Standards and Technology and the American Dental Association.

The specific material or materials that are developed are mercury-free amalgams; we have a CRADA with Densply at this time that will be working toward the manufacturing and production of that particular material. And we see a lot of benefit for additional materials that may come up following that same approach.

The Air Force study of Vietnam veterans is progressing, but we haven't come to closure with it. However, preliminary findings in taking a look at the exposure to mercury-containing amalgam in those individuals compared to some neurologic measures show no correlation.

Mr. PORTER. Thank you very much for your excellent testimony this morning. You did a wonderful job.

Dr. KLEINMAN. Thank you very much.

Mr. PORTER. The next two questions are for Dr. Varmus, and I ask these because I had to leave the hearing when you were here. One of them is a very sensitive subject that is bound to come up at some point during this year. And I'm very interested in your views.

Last year, you appointed an outside committee to advise you on the use of human embryos in research. That panel presented its recommendations to your Advisory Council last December. While the Council was meeting, President Clinton issued an Executive Order prohibiting certain kinds of embryo research from being conducted, which contradicted some of the panel's findings. Have you made a decision about the other recommendations of the panel which were not affected by the President's Executive Order? And if not, when should we expect a decision?

Dr. VARMUS. Well, you know, Mr. Porter, the President's statement directed that we not fund research on embryos that were created expressly for research purposes. It did not exclude research that would be carried out with so-called "spare embryos," those embryos that are left over from procedures that were intended to develop embryos to be implanted for therapeutic purposes and were given to investigators with the consent of the donors of gametes.

Research of that type could be incorporated into eight research proposals that are currently being funded but the investigators who are receiving the funds are not permitted at this stage to do research with such "spare embryos."

When the results of our embryo research panel were presented to my advisory committee on December 1st and 2nd, my advisory committee recommended that the NIH develop a standing panel, not unlike the Recombinant DNA Advisory Committee, that would do a number of things. It would advise me about our general policy in this area, it would further our efforts in public education about the pre-implantation embryo research, and the use of early embryos in research and therapy, and it would provide an ongoing means to review applications that might be funded in this area, as recommended originally by our panel.

I'm in the process now of trying to recruit members of this standing panel. We hope to have that panel in place some time in this coming year. That panel will be asked to do the things I've just listed. And it will then come to terms with those few applications that might be supporting research on so-called "spare embryos."

Mr. PORTER. Thank you. The second question deals with indirect costs. They are likely to be a target for some this year, given the current cost cutting environment. The Administration has announced proposals to make some fairly modest changes in the current indirect cost system, most of which would not take effect in 1996.

What is your response to those who advocate more dramatic changes, such as making NIH a prudent purchaser, that is, awarding grants to institutions with lower indirect cost rates? With so many high-quality grants going unfunded, would there be much impact on the quality of your research portfolio?

Dr. VARMUS. Yes. I would take a dim view of that approach. On the other hand, I would point out to you that in response to a Congressional directive some years ago, we do include for review by our study sections the total costs of grants. That is, grant reviewers are not simply shown what we consider now the project costs, but also the total costs, which include the two additional elements, the administrative costs and the facilities costs. So that total request is taken into consideration during the review process, as was first directed by this committee some years ago.

My view is that we need to recognize publicly that what were previously called indirect costs are real costs of doing research. For institutions to carry out their research mission, they have to supply administrative functions and facilities for doing the research. So these are actual costs of research. We also need to recognize that rates vary, especially with respect to facilities costs. As you know, administrative costs were capped a few years ago at 26 percent. So the major variation among institutions is due to difference in facilities costs.

One of the outcomes of the Administration's directives in this area will be to promote an understanding of those facilities costs. The NIH and the Department of HHS are heavily involved in a study of that kind that will attempt to understand how the Government is charged for facilities, for utilities, for special services like animal costs, for building, and for compensation for interest rates. We hope, with a deeper understanding of how facilities costs come to vary, that we'll be able to develop some benchmarks to analyze more carefully how such facilities are used, and to maximize our savings in this area.

But I would be loath to suggest that the facilities costs should become a major determinant in decisions about the research that we're going to fund. We know very well from even a cursory examination of the data that some of our most prestigious and productive research establishments are places where the facilities costs are extremely high. And we need to understand that more fully, rather than run the risk of decreasing research activities at those places that have been especially productive over many years.

Mr. PORTER. Dr. Varmus, thank you very much for answering those two additional questions on the record. Dr. Kleinman, thank you for your good testimony, once again. And Dr. Slavkin, we look forward to hearing from you next year.

Thank you all very much. The subcommittee will stand in recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

GENE THERAPY

Mr. Obey: I understand your researchers are involved in gene therapy research. Could you explain the area and the possible implications for health improvements down the road?

Dr. Kleinman: Our investigators are exploiting the fact that the oral cell and tissues are readily accessible and would therefore be good candidates for genetically based therapies. With salivary gland cells, for example, if we can master methods for inserting genes into salivary gland cells, we can turn the cells into mini-factories producing a desirable gene product that will be continuously released in saliva. We have already accomplished this in animal studies. Our investigators inserted a gene for a potent antifungal agent, histatin, in rat salivary glands; the gene was expressed, and histatin showed up in the saliva. (Histatin is not normally a component of rat saliva.) If further research shows that this approach is feasible in human studies, we will have a novel treatment for candidiasis, a serious fungal infection common in AIDS patients and other patients with immunodysfunction. Our investigators are also exploring this type of approach in the treatment of periodontal diseases. In this example, the gene inserted would produce a protein that would compete with a molecule on the surface of periodontal disease-causing bacteria that enables the bacteria to colonize oral tissues.

Interestingly, salivary gland cells can be engineered to secrete gene products into the bloodstream. We are conducting studies in collaboration with the National Institute of Child Health and Human Development on inserting the gene for human growth hormone in salivary cells in such a way that the hormone is released into the circulation. In addition to salivary cells, dental investigators have established that functioning genes can be inserted in skin cells and tongue muscle cells. We call this kind of gene therapy gene "therapeutics," because we are using genes to deliver a gene product of use to the body in treating a disease.

We are also conducting gene therapy research to restore function to damaged salivary glands. Such damage can occur in the case of salivary gland disease, or as a result of radiation to the head and neck. In these conditions the saliva-secreting cells may be destroyed but salivary ductal cells may be preserved. Our investigators are experimenting with genes that will alter the membranes of ductal cells from being water impermeable to water permeable, thus enabling them to become fluid-secreting cells.

PROGRESS IN BIOMATERIALS RESEARCH

Mr. Obey: Are you making any progress in biomaterials research? Can you tell us about these efforts?

Dr. Kleinman: Our current $13 million program in biomaterials research and development includes a wide range of basic and clinical studies on existing and new materials to determine their biocompatibility, safety, efficacy, durability, esthetics, ease of handling, and patient satisfaction. Progress is being made on several fronts, ranging from computer-assisted design and manufacture of restorations, to true "biomaterials" where molecular approaches to tissue regeneration are being studied in animal models.

Improvements are being made in disease prevention using adhesive materials that can protect and seal the entire tooth crown and roots from decay, and in diagnosis with the development of materials used to line cavity preparations which change color if tooth decay begins to recur. There also is progress in research investigating the interaction of materials with biologic repair, such as the use of calcium phosphate cements, which provide a scaffold for bone regeneration. Animal studies using bone morphogenetic proteins to stimulate the regeneration of jaw bone, dentin, and periodontal structures are showing great promise.

We have been collaborating with the National Institute of Standards and Technology and the American Dental Association in the development of a mercury-free restorative material. This research has advanced to the stage where there is collaboration with the private sector for further research and development of the product. We should be able to proceed to clinical trials in several years.

ORAL CANCER

Mr. Obey: Please give the subcommittee an update on steps being taken to address oral cancer by your institution.

Dr. Kleinman: Estimates for 1995 indicate that there will be over 28,000 new cases of oral cancer diagnosed and over 8,000 oral cancer deaths. The incidence of oral cancers is more than twice as high in men as in women and more frequent in men over 40. Overall, the 5-year survival rate is 52 percent, with racial differences: Between 1983 and 1990 the survival rate was 55 percent for whites and 34 percent for African-Americans.

As is the case with many other cancers, oral cancers are multifactorial in origin, with genetic factors interacting with exposure to a variety of environmental factors including tobacco, alcohol, viruses such as the human papillomavirus, and dietary factors. The malignant transformation of cells is thought to come about by a combination of attacks or "hits" to the cells that affect cellular genes, including so-called tumor suppressor genes.

In addition to basic research to elucidate the steps in the pathogenic process and explore what can be done to reverse them, we are collaborating with other Federal agencies in a number of clinical studies. With the National Cancer Institute (NCI) we are: 1) investigating risk factors in the Commonwealth of Puerto Rico (where the incidence of oral cancer is higher than on the U.S. mainland); 2) examining outcomes and regional variation associated with alternative therapies for oral cancer in patients 65 and older; and 3) analyzing an NCI/Health Care Financing Administration database related to costs of oral cancer care. With the Department of Veterans Affairs (DVA) we are conducting a study of changes in biomarkers for malignant transformation seen in cells biopsied from precancerous oral lesions in DVA Medical Center patients.

We are currently issuing a Request for Applications for Oral Cancer Centers in order to bring together interdisciplinary teams of investigators to focus on all aspects of these cancers with the aim of developing better methods of diagnosis, treatment, and, ultimately, prevention.

In addition, the Institute is actively involved in informing and educating the public and health professionals about all risk factors, diagnostic procedures, consequences of treatment, and approaches to prevention. We provide information through our National Oral Health Information Clearinghouse, and we have also developed materials in collaboration with NCI, the Centers for Disease Control and Prevention, and the World Health Organization.

QUESTIONS SUBMITTED BY THE SUBCOMMITTEE

MERCURY-CONTAINING AMALGAMS

Mr. Dickey: What are your findings regarding the health effects of amalgam fillings (mercury fillings)?

Dr. Kleinman: In January 1995 the Dental Amalgam Subcommittee of the Public Health Service (PHS) Environmental Health Policy Committee reiterated the policy announced in January 1993 by the PHS following extensive reviews of the literature: Amalgam should not be banned or restricted in use. NIDR has been urged to expand research on amalgam as well as on alternatives to amalgam. We are following all research efforts on mercury--our own as well as other agencies, recognizing certain inherent difficulties in clinical studies: There are multiple sources of mercury in the environment in dental fillings, in foods such as fish, and in the air we breathe. Inorganic forms of mercury (used in fillings) may convert to organic forms (as in food) in the body, making it difficult to trace the source of mercury found in any body organ.

We are collaborating with the National Institute of Environmental Health Sciences, the Food and Drug Administration, and the Centers for Disease Control and Prevention, and professional organizations such as the American Dental Association (ADA) in research and surveillance activities.

One major effort is a collaboration with the Air Force in a study of Vietnam veterans for whom extensive dental and medical records exist. Our investigators have completed oral examinations and taken blood and urine samples to compare mercury levels in these fluids with a measure of the total years of exposure to mercury in dental fillings. While the mercury levels in these fluids is higher in individuals with more amalgam exposure, the amounts are very low and appear not to have any clinical significance. After investigating over 50 clinical conditions and symptoms so far, our preliminary analyses indicate no evidence that these levels of mercury are associated with disease involving the kidneys or the nervous system.

In other studies we have been collaborating with the National Institute of Standards and Technology and the ADA in the development of a mercury-free restorative material. This research has advanced to the stage where there is collaboration with the private sector for further research and development of the product. We are also planning a long-term clinical trial to determine if there are any cognitive effects in schoolchildren with amalgam fillings compared with children without amalgam fillings. Also under way is a study of in utero effects of mercury in an island population where fish with a high mercury content is an abundant part of the diet.

Our research portfolio on all restorative materials totals over $13 million, which includes a wide range of basic and clinical studies on existing and new materials to determine their safety, efficacy, durability, esthetics, ease of handling, and patient satisfaction.

PROGRESS IN PAIN RESEARCH

Mr. Dickey: I was interested to learn of the pain research conducted by NIDR. What recent advancements has NIDR made in the area of pain prevention?

Dr. Kleinman: There has been a long tradition of pain research in dentistry, dating to the first demonstrations of the anesthetic effects of nitrous oxide and ether by two dentists in the 19th century. Currently, NIDR conducts basic and clinical research on the anatomy, physiology, diagnosis, treatment, and prevention of acute and chronic pain. Our staff scientists direct the Pain Clinic in the NIH Clinical Center and are conducting research on patient volunteers with pain conditions not limited to the face or mouth. Major findings related to prevention include:

> Demonstration of the effectiveness of presurgical treatment using a nonsteroidal anti-inflammatory agent, combined with a long-lasting local anesthetic, in reducing the acute post-operative pain and inflammation following extraction of wisdom teeth.
>
> Evidence that, in patients undergoing surgery, those who receive general anesthesia as well as the application of a local anesthetic at the site of the incision, experience less severe post-operative pain of shorter duration than patients receiving general anesthesia only. It is thought that the local anesthetic blocks the bombarding of the central nervous system by pain-associated nerve signals, which act to sensitize the wound area, heightening the experience and duration of pain.
>
> New neuro-imaging studies of acute and chronic pain indicate that extensive areas of the brain are involved in the perception of pain. As investigators refine these maps and further detail the pathways and neurochemicals involved in the transmission and modulation of pain, the opportunities for the development of new kinds of pain-relieving compounds increase. For example, investigators have implicated a specific receptor called the NMDA receptor in mediating the severe and often intractable pain associated with nerve injury (neuropathy) and tissue injury. The drugs they have found that can block this receptor include the ingredient of a common cough suppressant and a drug used to treat Parkinson's disease. They believe that the use of a combination of agents working against different receptors along different pathways may provide the relief needed by chronic pain patients. Recently they have discovered a compound derived from marine cone snails that can relieve pain without causing numbness.

Our investigators recognize that pain is a complex phenomenon composed of sensations that can be described, localized, and judged in intensity, and also an emotion that reflects the suffering, stress, and meaning of the pain in the individual's life and what it may portend. A number of our studies are designed to explore the multiple dimensions of pain and develop treatment programs that address multiple factors. These studies are particularly important in preventing acute pain problems from becoming chronic.

Mr. Dickey: What benefits can be derived from NIDR's pain research in areas other than oral health?

Dr. Kleinman: Our investigators have demonstrated that the mechanisms governing pain in the oral and facial region are completely analogous to pain mechanisms seen in other parts of the body. It follows that much of the research to assess, diagnose, control, or prevent oral and facial pain apply to other painful sites in the body as well. For that reason, our investigators have been instrumental in the publication of new guidelines by the Agency for Health Care Policy Research (AHCPR) for the control of cancer pain and also acute pain following surgery. NIDR has also been asked to take the lead in a report to Congress on the frequency and associated health care costs for a number of chronic pain conditions, an effort which has led to a collaboration with NIH components and AHCPR.

Our research studies are also contributing to genetics and developmental biology studies by tracking how the nervous system develops and answering such questions as: What genes are involved in shaping the developing brain and in the movements and maturation of primordial nerve cells? How is the timing and movement of future nerve cells coordinated with those of other cells derived from the same embryonic cell layer--the ectoderm? What causes nerve cells to self-destruct in the course of development and aging? Our pain studies are also shedding light on the endocrine and immune systems, since research has shown that these cells share certain receptors and transmitter chemicals in common.

BONE AND JOINT

Mr. Stokes: To what extent has the research knowledge generated by your Institute in the area of facial bone and joint diseases led to advances in non-facial bone and joint diseases?

Dr. Kleinman: It should be recognized that, while many of the studies performed on bone and cartilage have been performed on tissue obtained from the oral cavity, many studies utilize these tissues from other parts of the skeleton. Although there may be site-specific differences depending on the origin, it is very clear that the data obtained are generally pertinent to all sites.

The Bone Research Branch of the NIDR was the first laboratory to establish the procedures to chemically isolate hard tissue proteins intact. These discoveries led to a virtually complete characterization of these important proteins and to the development of antibodies that are now used around the world, in particular in the development of biochemical markers to measure skeletal diseases.

In the same vein, a group of NIDR scientists were the leaders in describing a family of molecules termed the bone morphogenetic proteins--proteins which are now known to regulate bone and cartilage formation, and are of great potential therapeutic value. More recently, the group has identified cartilage-derived morphogenetic proteins that may be useful in cartilage repair.

Another NIDR scientist developed a bone cell culture system that can be applied to a variety of different animal species of different ages and from different skeletal sites. This procedure allows for the reproducible establishment of cells in the bone-forming lineage that serve as a model system for studying the steps in bone formation during normal development, and changes that occur in a number of genetic and acquired diseases. These cells have been used extensively within the Institute to isolate and characterize the genes that code for hard tissue matrix proteins, another area in which NIDR scientists were pioneers in the field. Current studies are now focusing on precursor (stem) cells within the bone marrow that give rise to a number of different tissues including bone and cartilage. Clinical protocols are under way to develop these cells for use in augmentation of bone and cartilage, not only in the oral cavity, but in other skeletal sites, and as a potential vehicle for gene transfer.

Mr. Stokes: How will the Institute's "new Bone Clinic" help to further advances in this broad area of research and national need? What are the implications for advances in bone marrow research in general?

Dr. Kleinman: Current activities in the NIDR's Bone Clinic are aimed at determining 1) the conditions for _in vitro_ expansion of a population of cells that support bone formation, and 2) the appropriate solid carriers that can be used to place these cells into a bony defect and bring about new bone formation. Definition of these two variables will eliminate a number of problems that exist in current procedures by using the patient's own cells and synthetic carriers that will not elicit an immunological response.

The science behind these clinical projects is aimed at characterizing the different members of the marrow stromal population of cells. Although it is known that this population of cells contains precursors for a variety of tissues including bone and cartilage, fat, and hematopoiesis supporting stroma, virtually nothing is known about what controls their activation and commitment to one cell type or another. Studies are aimed at determining if there are markers by which different precursors can be separated from one another by cell sorting, characterizing the factors that support their proliferation but maintain their undifferentiated state, and identifying the factors that trigger their differentiation into a particular cell type. With this basic information, it should be possible to establish a method for regeneration of a number of connective tissues.

In addition, it should be recognized that hematopoiesis is absolutely dependent on a normal complement of bone marrow stromal cells. Changes in the normal relationships result in disease, such as osteoporosis, and perhaps in certain types of diseases where there are abnormal forms of hematopoiesis. Consequently, the knowledge of how the marrow stroma directs hematopoiesis provides possible avenues of therapy or intervention. These cells may also be valuable as a vehicle for gene transfers such that a missing gene is replaced in this population with "stem cell" properties.

NEUROLOGICAL RESEARCH

Mr. Stokes: A few weeks ago, the Committee had the opportunity to hear testimony from the Nation's Nobel Laureates. We welcomed the insight they provided on the status of the Nation's biomedical research enterprise. They indicated that neurological research was one of the most important areas that--if enhanced, offered considerable opportunity to further medical advances. To what extent does this statement apply to the research conducted by your Institute?

Dr. Kleinman: The NIDR has had a long interest in neurological research, particularly in the study of the response of the nervous system to injury as well as in the area of neural development. The common thread to this research is the involvement of special receptors in the spinal cord and brain whose activation leads to long-term changes in brain function associated with development, learning, and the response to injury. One of these receptors is the N-methyl-D-aspartate or NMDA receptor, which is activated by the release of excitatory amino acids such as glutamate and aspartate from the spinal cord terminals of peripheral nerve fibers that signal tissue damage. Activation of the receptor leads to hyperexcitability in the spinal cord and an amplification of pain. This increase in pain can be blocked by drugs that block action at this receptor. Such NMDA receptor antagonists hold considerable promise for the future development of new agents for the management of persistent pain produced by tissue and nerve injury.

Mr. Stokes: What is the extent of the Institute's investment in this particular area of research in FY 1996? How does this compare with FY 1995 and 1994?

Dr. Kleinman: In FY 1996, the NIDR expects to invest approximately $18 million in neurological research, compared to an estimated $17.5 million in FY 1995 and actual obligations of $17.2 million in FY 1994.

MINORITY HEALTH

Mr. Stokes: As you know, I have been following your Institute's initiative to develop a series of regional centers for minority oral health. According to the justification, participating institutions were awarded planning grants to initiate research studies. What progress are we making and what's the next phase of this effort?

Dr. Kleinman: In Phase I, the NIDR funded six planning grants in FY 1992 for Regional Research Centers for Minority Oral Health (RRCMOH) to improve minority health, increase the number of minority research investigators, and enhance infrastructure in minority institutions. The grants were awarded to minority dental schools, or to schools serving large minority populations, in collaboration with research-intensive institutions: (1) Charles R. Drew University of Medicine and Science with UCLA; (2) Howard University in Washington D.C. with the University of Maryland; (3) Meharry College of Dentistry in Nashville with the University of Alabama; (4) New Jersey Dental School, University of Medicine and Dentistry, with the University of Connecticut School of Dental Medicine; (5) New York University College of Dentistry with Forsyth Dental Center, Boston; and (6) St. Mary's University in San Antonio with the University of Texas Health Science Center Dental School.

Studies initiated within the centers focus on minority-related research topics, such as oral cancer, AIDS, and diabetes, and on lifestyle in relation to oral health in the community. NIDR also initiated a science program at the annual meeting of RRCMOH directors (co-sponsored by the NIH Office of Research on Minority Health), which emphasized the work of young minority investigators associated with the program.

Phase II of this initiative will fund similar collaborations for 5 years, using the Specialized Center mechanism. The FY 1995 competition is open to Phase I grantees and other applicants.

ORAL CANCERS

Mr. Stokes: How extensive is the problem of oral cancers and what steps are being taken by the Institute to address this health problem?

Dr. Kleinman: Estimates for 1995 indicate that there will be over 28,000 new cases of oral cancer diagnosed and over 8,000 oral cancer deaths. The incidence of oral cancers is more than twice as high in men as in women and more frequent in men over 40. Overall, the 5-year survival rate is 52 percent, with racial differences. Between 1983 and 1990 the survival rate was 55 percent for whites and 34 percent for African-Americans.

As is the case with many other cancers, oral cancers are multifactorial in origin, with genetic factors interacting with exposure to a variety of environmental factors including tobacco, alcohol, viruses such as the human papillomavirus, and dietary factors. The malignant transformation of cells is thought to come about by a combination of attacks or "hits" to the cells that affect cellular genes, including so-called tumor suppressor genes.

In addition to basic research to elucidate the steps in the pathogenic process and explore what can be done to reverse them, we are collaborating with other Federal agencies in a number of clinical studies. With the National Cancer Institute (NCI) we are: 1) investigating risk factors in the Commonwealth of Puerto Rico (where the incidence of oral cancer is higher than on the U.S. mainland); 2) examining outcomes and regional variation associated with alternative therapies for oral cancer in patients 65 and older; and 3) analyzing an NCI/Health Care Financing Administration database related to costs of oral cancer care. With the Department of Veterans Affairs (DVA) we are conducting a study of changes in biomarkers for malignant transformation seen in cells biopsied from precancerous oral lesions in DVA Medical Center patients.

We are currently issuing a Request for Applications for Oral Cancer Centers in order to bring together interdisciplinary teams of investigators to focus on all aspects of these cancers with the aim of developing better methods of diagnosis, treatment, and, ultimately, prevention.

In addition, the Institute is actively involved in informing and educating the public and health professionals about all risk factors, diagnostic procedures, consequences of treatment, and approaches to prevention. We provide information through our National Oral Health Information Clearinghouse, and we have also developed materials in collaboration with NCI, the Centers for Disease Control and Prevention, and the World Health Organization.

Mr. Stokes: How much is included in the FY 1996 budget request for this area of research? How does this compare with FY 1995 and 1994?

Dr. Kleinman: The Institute's investment in cancer research is expected to reach $8.1 million in FY 1996, compared to an estimated $7.8 million in FY 1995 and actual expenditures of $7.6 million in FY 1994. The majority of the NIDR cancer portfolio is devoted to research into oral cancers.

BIOMATERIALS

Mr. Stokes: What is the significance of the Institute's research on mercury-containing dental material, and what does the Institute hope to learn from its collaborative study with the U.S. Air Force on the health effects of mercury-containing amalgams?

Dr. Kleinman: While dental amalgams have been in use for dental fillings for over 150 years, only in the last decade have techniques been available to detect that a small amount of mercury vapor is released in the mouth in the course of chewing food. There is no evidence that exposure to this level of mercury vapor is harmful, and the Public Health Service has recently reiterated its policy, stated

2 years ago after an extensive review of the literature, that amalgams should not be banned or restricted in use.

NIDR was urged to expand research in this area and also to explore alternatives to amalgam. One major effort is a collaboration with the Air Force in a study of Vietnam veterans for whom extensive dental and medical records exist. Our investigators have completed oral examinations and taken blood and urine samples to compare mercury levels in these fluids with a measure of the total years of exposure to mercury in dental fillings. While the mercury level in these fluids is higher in individuals with more amalgam exposure, the amounts are very low and appear not to have any clinical significance. After investigating over 50 clinical conditions and symptoms so far, our preliminary analyses indicate no evidence that these levels of mercury are associated with disease involving the kidneys or the nervous system.

Mr. Stokes: Are we making any progress in biomaterial research and development? How close are we to having medically safe and mercury-free dental fillings?

Dr. Kleinman: Our current $13 million program in biomaterials research and development includes a wide range of basic and clinical studies on existing and new materials to determine their biocompatibility, safety, efficacy, durability, esthetics, ease of handling, and patient satisfaction. Progress is being made on several fronts, ranging from computer-assisted design and manufacture of restorations, to true "biomaterials" where molecular approaches to tissue regeneration are being studied in animal models.

Improvements are being made in disease prevention using adhesive materials that can protect and seal the entire tooth crown and roots from decay, and in diagnosis with the development of materials used to line cavity preparations which change color if tooth decay begins to recur. There also is progress in research investigating the interaction of materials with biologic repair, such as the use of calcium phosphate cements, which provide a scaffold for bone regeneration. Animal studies using bone morphogenetic proteins to stimulate the regeneration of jaw bone, dentin, and periodontal structures are showing great promise.

We have been collaborating with the National Institute of Standards and Technology and the American Dental Association in the development of a mercury-free restorative material. This research has advanced to the stage where there is collaboration with the private sector for further research and development of the product. We should be able to proceed to clinical trials in several years.

COLLABORATION

Mr. Stokes: Is the Institute's research dedicated to finding the genes associated with disfiguring birth defects a joint collaborative effort with the Child Health Institute, and what is the significance of this research?

Dr. Kleinman: NIDR and the National Institute of Child Health and Human Development (NICHD) share an interest in genetic disease affecting children and exchange information through the regular informal contacts among staff scientists and grantees, through the newly formed research interest groups on the campus, such as the hard tissue disorders club, and through our liaison with patient groups concerned with these disorders. Our Institutes are collaborating in a multi-Institute Request for Applications to map and sequence the rat genome, which can be expected to provide much valuable information about genes that are highly conserved in evolution and that are associated with the development of the head and facial structures.

We are currently planning a workshop, with support from the Office of Rare Disease Research, on the ectodermal dysplasias. These are hereditary disorders affecting hair, skin, teeth, and sweat glands, and we will invite collaboration with NICHD and other concerned organizations. We consider research on birth defects involving the head and face to be of high priority because they are among the most commonly seen. For example, clefts of the lip or palate occur as often as 1 in 700 births.

CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and have yielded comparable economic savings. What level of funding is included in the FY 1996 budget for clinical trials? How many trials would be funded? How many of these trials are new and how many are ongoing?

Dr. Kleinman: The FY 1996 budget request would provide $5.1 million for approximately 21 clinical trials, including 3 new projects and 18 on-going trials.

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously? Is there a specific system in place for dissemination of such information? Explain.

Dr. Kleinman: NIH uses a physician alert system when results of a clinical trial need to be communicated as soon as possible to the public--either because the preliminary findings are so positive that the trial is discontinued in order to extend the benefits of the experimental intervention to all patients, or when a trial is discontinued because of untoward side effects.

NIDR reports the results of clinical trials in peer-reviewed dental journals, through news releases and media coverage, at scientific meetings and consensus development conferences, and through the distribution of materials directly to the public and health care providers by the Institute or its newly established National Oral Health Information Clearinghouse. In addition, NIDR has initiated a series of symposia on Scientific Frontiers in Clinical Dentistry, a continuing education program for dental care personnel to provide updates on advances in dental research that have immediate relevance to dental practice--including the results of clinical trials.

In pain research, NIDR clinical studies and trials have been instrumental in the development of two new clinical guidelines published and widely distributed by the Agency for Health Care Policy Research: One is on the management of acute post-operative pain; the second is on the management of cancer pain.

A strong alliance between the Institute and professional and public organizations exists; the latest information is routinely provided to these groups and their members, and NIDR staff meet with these organizations several times a year. Policy statements, newsletters, and journals are used effectively, and we are currently exploring electronic information systems, such as the Internet.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine 5-year increments, to what extent has the success rate remained relatively flat over the past 5 to 10 to 15 years? Explain.

Dr. Kleinman: The success rates for NIDR remained at 34 percent in FY 1985 and FY 1986, then dropped to 29 percent in FY 1987, and again remained relatively constant from FY 1988 through FY 1990 when the rate ranged from 25 to 21 percent. In FY 1991, the NIDR success rate was back up to 30 percent, with decreases in the next 3 years ranging from 24 to 28 percent. The average success rate for the entire period was 28 percent.

Fluctuations in success rates are a reflection of several factors:

- Within the total amount available each year for competing grants, changes in the mix of grant types can have significant bearing on the number of awards that can be made; for example, average costs of the large program project grants are about $650,000, compared to the traditional grants at about $190,000, and FIRST awards are under $100,000. Clearly, if a higher-than-normal number of program project grants is awarded, this reduces the overall number that can be funded, thus reducing the success rates.

- The cyclical nature of the grant process is such that, in some years, commitments to fund noncompeting grants are significantly higher or lower than average, thus limiting (or increasing) the number of competing awards that can be made.

- The length of grant awards can also have some impact; if a higher than average number of 5-year awards are made in a given year, this increases noncompeting commitments for a longer period of time and consequently limits the number of competing awards that can be made in future years.

- o Prior to the implementation of the NIH Cost Management Plan, which eliminated downward negotiations for noncompeting awards, the success rate could fluctuate, depending on the downward negotiation rates applied to noncompeting awards.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Kleinman: The trend in the average cost of competing research project grants over the last 10 years--in both current and constant dollars--is shown below.

	Average Cost ($000)	
Fiscal Year	Current Dollars	Constant Dollars
1985.......	$121	---
1986.......	122	$117
1987.......	155	141
1988.......	162	141
1989.......	161	133
1990.......	160	125
1991.......	178	133
1992.......	190	136
1993.......	175	121
1994.......	187	124

Fluctuations in average cost are a result of the same factors for swings in success rates as described above.

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Kleinman: Federal mandates require that all questions related to race and gender be identified as optional on all NIH research grant applications. As a result, we are unable to identify accurately either the number of applications submitted by minorities and women or the number of awards to minorities and women. For example, in 1994, over 21 percent of applicants chose not answer the optional questions.

With regard to HBCUs, this Institute receives very few applications--averaging less than four each year for the last 10 years. Therefore, data on success rates are not meaningful.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average cost of research project grants awarded to women? To minority researchers? To African American researchers? To HBCUs?

Dr. Kleinman: For the reasons stated above, it is not possible to provide accurate or meaningful data on average costs of research project grants awarded to the groups specified.

FTEs

Mr. Stokes: Is the Institute currently under a FTE freeze, and if so, how long has it been under this freeze? How is it impacting operations?

Dr. Kleinman: The NIH, including NIDR, had been under a Public Health Service (PHS) agency-wide hiring freeze, limiting hires to personnel within the PHS, since December 1993. The freeze was lifted in February 1995. As a result of the freeze, NIDR lost 16 percent of its strength and is now facing substantial difficulties in recruiting individuals with the necessary skills and experience required of a highly sophisticated research program with national leadership responsibilities.

We remain concerned that the hiring freeze created distortions in staffing skill mixes, which have had significant effects on the type, amount, and quality of research that can be performed, as well as on our administrative responsibilities, the processing and management of grant and contract awards, and the stewardship of public funds. However, like the rest of the Federal government, NIH is not exempt from the pressures of the Federal Workforce Restructuring Act and the requirements of the Administration's streamlining goals. Under the leadership of the Vice President, NIH including this Institute will continue to develop ideas and options for effectively managing our programs in this changing environment.

FEDERAL ROLE IN INTRAMURAL RESEARCH

Mr. Stokes: In light of continuing fiscal constraints, in your professional judgment, why must the Federal role in intramural research continue?

Dr. Kleinman: Intramural research has been vital to the dental research enterprise. As an Institute we began with an intramural program only. It was the early work of these staff scientists that put dental research in America on a sound footing, achieving pivotal discoveries with regard to the causes of the major dental diseases and the role of fluorides in prevention. As the Institute grew, intramural investigators played a lead role in laying the foundation for hard tissue research, craniofacial developmental biology, microbiology and immunology research, studies of pain, oral epidemiology and behavioral sciences, and other fields special to oral science. Many senior scientists in universities and research institutions were trained in the intramural program, which continues to be a strong force for nurturing talent in the oral sciences.

The NIDR intramural program today continues to be a source of innovation and leadership in the oral health research community, able to embark on high risk research over long periods of time. Examples of the payoff of such research efforts include the discoveries of bone and cartilage genes and families of growth proteins, a component in saliva that confers protection against the AIDS virus, and the development and testing of new kinds of drugs and drug combinations for the relief of acute and chronic pain.

Further, the existence of staff scientists from many components of NIH on the campus makes it possible for day-to-day exchange of ideas, information, and materials such as reagents used in research. Our investigators can also share in the use of unique and expensive instruments and equipment, and have access to patients with complex and often rare diseases who volunteer for study in the Clinical Center. NIDR also is able to conduct independent research as well as serve as a resource to all other Institutes and Centers and the extramural community through our direction of the Pain Clinic and the Dental Clinic. Our future plans call for collaborations with other NIH components, the academic community, and the private sector in connection with our newly formed Bone Clinic.

AIDS RESEARCH PROGRAM

Ms. Pelosi: The budget justification refers to the discovery of a protein in saliva that may hamper the AIDS virus. Will the researchers at NIH be able to use that finding to develop a vaccine or effective treatments for HIV disease? Are there any other new findings with regard to AIDS at NIDR?

Dr. Kleinman: Our investigators have found that a small protein produced in saliva, secretory leukocyte proteinase inhibitor (SLPI), inhibits HIV from entering immune cells in test-tube studies. Their experiments indicate that SLPI does not attack the virus directly, but acts on white blood cells to prevent viral entry. The discovery of SLPI came about when our investigators, intrigued by the evidence that AIDS is rarely spread through oral contact, tested a variety of components of saliva and found SLPI to be the only compound effective at levels normally present in saliva. They are now studying how SLPI works at the molecular level. They also note that SLPI is present in fairly high concentration in saliva, tears, and bronchial fluids, whereas levels in blood and rectal fluid are below what is necessary for viral inhibition.

Possible therapeutic uses of SLPI include its use as a topical cream or jelly to prevent HIV infection during sexual intercourse or as a treatment of HIV-infected individuals, in which case SLPI would be injected into the bloodstream to prevent HIV in circulation from invading white blood cells. Gene therapy in which the gene for SLPI would be inserted into cells to augment production of SLPI is also a possibility.

Other NIDR advances in AIDS research include the finding that oral lesions are common in HIV disease, with candidiasis and hairy leukoplakia the most frequently seen oral opportunistic infections. When individuals with similar depletions of T4 immune cells are compared, those with oral candidiasis progress more rapidly to AIDS than individuals without the oral lesions. Our epidemiology studies are documenting the frequency and pattern of oral manifestations of HIV disease in different patient groups. These studies include our collaboration with the National Institute of Allergy and Infectious Diseases in the Women's Interagency HIV Study to allow comparisons of oral findings in relation to the stage of HIV disease and other HIV-related pathology in women.

We are currently conducting a controlled clinical trial to determine if rigorous oral hygiene, including daily use of an antimicrobial mouth rinse, and bimonthly professional care can reduce or prevent oral complications in HIV patients with severe immunosuppression. In other clinical research, our investigators have observed that oral epithelial cells can be infected with HIV, even though these cells lack the surface receptor (CD4) that characterizes the immune cells that are targeted by HIV. While SLPI may protect the oral cavity from invasion by HIV, other mucosal sites may lack this protection--in which case infected mucosal epithelial cells at these sites may serve as a reservoir of infection.

Our focus on the oral cavity and saliva has also paid off in research showing that salivary gland cells can be used as vehicles for gene therapeutics. We have shown that the gene for a potent antifungal agent, histatin, can be inserted into the salivary gland cells of animals so that the cells become local factories producing histatin for release in saliva. One of the first applications of this research would be to treat candidiasis in immunosuppressed individuals, including patients with AIDS.

SALIVA AS A DIAGNOSTIC TOOL

Ms. Pelosi: It appears that NIDR-supported research is identifying ways to use saliva to assess various aspects of health, much as blood has been used in the past. In general, what do you see as the promise of using saliva as a diagnostic tool in medicine?

Dr. Kleinman: For both practical and theoretical reasons, we see great potential for saliva as a diagnostic tool. First, saliva is readily accessible and convenient; its collection does not entail invasive procedures such as drawing blood or the availability of toilet facilities necessary for collecting urine samples. Thus, the use of saliva should be cost-effective and should enable investigators to screen individuals in field studies or areas lacking medical facilities.

Second, saliva has been shown to reflect levels of a number of molecules of interest in circulation, including hormones, nutrients such as fats, medications, alcohol and other recreational drugs, certain infectious organisms, and antibodies. Commercially available kits using saliva are available for HIV antibodies, viral hepatitis, alcohol, therapeutic agents such as theophylline, lithium, methadone, and cyclosporine, and markers of salivary gland disease, including cystic fibrosis and Sjögren's syndrome. Under development are salivary markers that might indicate risk for oral cancer such as specific oncogenes, stress proteins, and other molecular markers related to repair of DNA.

OSTEOPOROSIS AND BONE CONDITIONS

Ms. Lowey: I am aware of the NIDR's research on osteoporosis and other bone conditions. Can you provide an update on the developments in your research on osteoporosis and other bone conditions?

Dr. Kleinman: Along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, we recently sponsored a workshop that examined the relationship between oral bone loss with the bone loss seen in osteoporosis. We are following up on that workshop with a Request for Applications for further studies in this area. Oral bone loss, detectable in a dental visit, may be an early warning sign for osteoporosis, and we need more research to explore this hypothesis.

We are also reviewing proposals for a contract to investigate oral hard tissue status in relation to skeletal bone mineral density measures and osteoporosis in a sample of women enrolled in the NIH Women's Health Initiative. Other studies related to osteoporosis and other bone conditions are looking at periodontal diseases in relation to osteoporosis and the role of fluorides, vitamins, and hormones in bone growth and in the treatment or prevention of bone loss. We are also studying cartilage and connective tissue diseases more prevalent in women, such as rheumatoid arthritis.

We have an extensive basic research portfolio, which has made major contributions to our understanding of the genes and proteins involved in bone growth and turnover and has identified the genetic defects associated with hereditary bone and tooth diseases. Our investigators are among leading researchers who have discovered families of bone and cartilage growth factors--so-called "morphogenetic proteins," which are being studied for potential use to build new bone, to enhance fracture repair, and for use in other orthopedic and dental purposes. Among the more interesting findings from basic research are that bone cells taken from older individuals show declines in the production and pattern of essential bone proteins when compared with cells taken from younger individuals.

To move findings of basic research into the clinical arena, NIDR has established a Bone Clinic in the NIH Clinical Center. Studies have already begun on ways by which a patient's own bone marrow cells could be removed, expanded in tissue culture, and then re-implanted in order to build new bone. Future protocols for the Bone Clinic will involve collaboration with other NIH components and the extramural community.

WOMEN AND JOINT DISORDERS

Ms. Lowey: I am aware of your efforts on behalf of those who suffer from disorders of the jay joint...called TMD. As you state in your testimony, women are affected disproportionately by the pain and dysfunction associated with TMDs. I understand from your testimony that NIDR is working to clarify the diagnoses of TMDs and is supporting preventive and conservative treatments for TMDs. Can you tell us more about this work and bring us up to date on your progress in this area?

Dr. Kleinman: Data from an NIDR survey found that as many as 10 million people experience episodes of orofacial pain more than once during any 6-month period. More than twice as many women than men reported these symptoms. In addition, women seek treatment for these conditions six times more frequently than men.

Temporomandibular disorders (TMDs) are orofacial pain disorders involving the jaw joint and muscles of mastication. Because research on these disorders has been hampered by the lack of standardized diagnostic criteria, NIDR funded the design of "Research Diagnostic Criteria for Temporomandibular Disorders" and the ensuing calibration and reliability testing. An application to evaluate their validity is currently under review. NIDR is supporting a study comparing surgical versus nonsurgical therapies, such as drugs, splints, and physical therapy, in the management of patients with internal derangement of the temporomandibular joint (TMJ).

Another NIDR-sponsored research project has resulted in the identification of the miniature pig as an excellent animal model for TMD research. Its structure and masticatory patterns are surprisingly similar to that of the human. Research using this model will permit experimental studies on the long-term consequences of disc displacement and controlled studies of surgical and nonsurgical procedures to repair joints, reduce pain, and preserve joint function.

A long-standing interest in pain (NIDR manages the NIH Pain Clinic) has led the Institute to advocate reversible, noninvasive approaches to treating these disorders. NIDR, therefore, has supported research that enhances our capacity to manage pain through combinations of drugs, as well as nonpharmacological interventions. The Institute is also supporting research to evaluate the impact of low-cost, early patient education in simple self-help strategies that avoid irreversible therapies, such as surgery.

NIDR-supported investigators have identified a potential biomarker in the synovial fluid of the TMJ that may indicate cartilage and disc degeneration in patients with osteoarthritis. These investigators believe that arthritis of this joint is a major factor in TMD disorders.

We also designed a series of TMD-related initiatives. For example, the Institute sponsored workshops, including the first International Workshop on the TMDs and Related Pain Conditions in April 1994. This meeting laid the groundwork for research that can be pursued immediately.

NIDR is also interested in addressing patient and provider educational needs directly. To that end, the NIDR-supported National Oral Health Information Clearinghouse distributes a package of information about the TMDs to patients and practitioners.

The Institute sponsors a series called Scientific Frontiers in Clinical Dentistry, which are symposia aimed at the continuing dental education of practitioners, with updates on the diagnosis and management of the TMDs.

In addition, NIDR is planning a technology assessment conference on TMD management for spring 1996, and has issued a Request for Applications to study the etiology and pathogenesis of the TMDs.

JUSTIFICATION OF THE BUDGET ESTIMATES

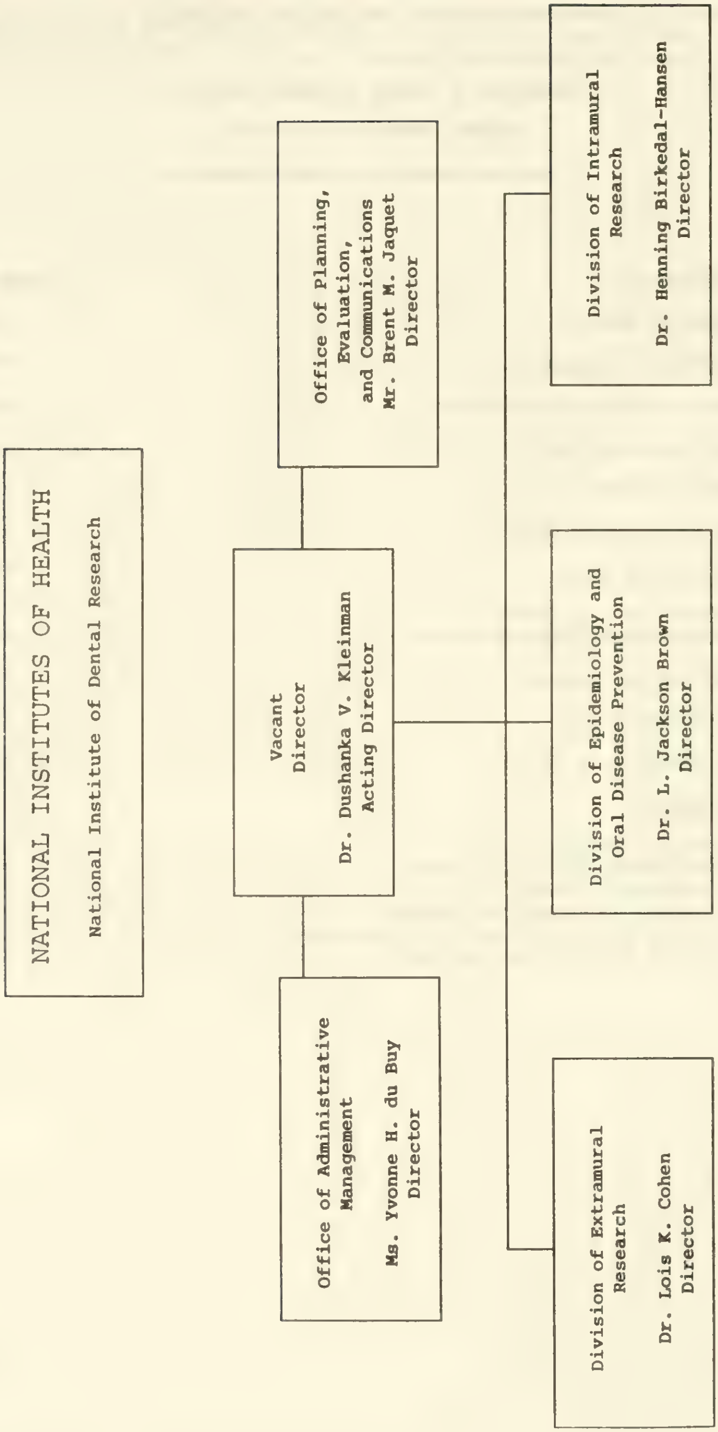
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

FY 1996 Budget	Page No.
Organization chart	186
Appropriation language	187
Amounts available for obligation	189
Budget mechanism table	190
Summary of changes	192
Budget authority by object	194
Administrative costs	196
Significant item in Senate Appropriations Committee reports	197
Authorizing legislation	198
Appropriation history	199
Budget authority by activity	201
Justification:	
A. General statement	203
B. Extramural research programs	207
C. Intramural research	210
D. Research management and support	212
E. Detail of full-time equivalent employment (FTE)	213
F. Detail of end-of-year employment	214

186


NATIONAL INSTITUTES OF HEALTH
National Institute of Dental Research
Office of Administrative Management
Ms. Yvonne H. du Buy
Director
Vacant
Director
Dr. Dushanka V. Kleinman
Acting Director
Office of Planning, Evaluation, and Communications
Mr. Brent M. Jaquet
Director
Division of Extramural Research
Dr. Lois K. Cohen
Director
Division of Epidemiology and Oral Disease Prevention
Dr. L. Jackson Brown
Director
Division of Intramural Research
Dr. Henning Birkedal-Hansen
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to dental diseases, [$162,832,000] *$168,341,000*.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

National Institute of Dental Research

Amounts Available for Obligation [1]

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$169,520,000	$162,832,000	$168,341,000
Section 205 Procurement reduction....................		-109,000	
Section 207 Rent reduction......		-2,000	
Section 513 S&E reduction.......		-74,000	
Subtotal, adjusted appropriation.............	169,520,000	162,647,000	168,341,000
Comparative transfer to:			
Office of AIDS Research, NIH, for HIV activities...........	-12,185,000		
Comparative transfer from:			
Other NIH Institutes for Management Fund adjustment.....	+826,000	+821,000	
Subtotal, adjusted budget authority................	158,161,000	163,468,000	168,341,000
Unobligated balance, lapsing....	-30,000	---	---
Total obligations.............	158,131,000	163,468,000	168,341,000

---

[1] Excludes the following amounts for reimbursable activities carried out by this account: FY 1994 -- $1,928,000; FY 1995 - $3,000,000; and FY 1996 - $3,000,000.

Also excludes funding for HIV activities: FY 1995 - $11,745,000; FY 1996 - $12,309,000, included in Office of AIDS Research, NIH.

Note: Excludes $58,000 in FY 1994 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects:						
Noncompeting	293	$53,723,000	350	$57,651,000	346	$57,303,000
Administrative supplementals	(30)	1,077,000	(33)	1,223,000	(33)	1,361,000
Competing:						
Renewals	48	9,478,000	34	7,061,000	37	7,984,000
New	130	13,208,000	105	12,236,000	106	12,150,000
Subtotal, competing	178	22,686,000	139	19,297,000	143	20,134,000
SBIR/STTR	14	2,124,000	17	2,646,000	17	2,773,000
Subtotal, research projects	485	79,610,000	506	80,817,000	506	81,571,000
Research Centers:						
Specialized/comprehensive centers	29	18,890,000	27	20,734,000	27	21,605,000
Other Research:						
Research career programs	112	7,784,000	112	8,083,000	112	8,317,000
Minority biomedical support		138,000		196,000		202,000
Other research	13	1,026,000	12	1,037,000	12	1,067,000
Subtotal, other research	125	8,948,000	124	9,316,000	124	9,586,000
Total, research grants	639	107,448,000	657	110,867,000	657	112,762,000

Research Training:						
Individual awards:						
Noncompeting	14	405,000	7	198,000	22	657,000
Competing	7	186,000	15	440,000	--	---
Subtotal, individual	21	591,000	22	638,000	22	657,000
Institutional awards:						
Noncompeting	145	4,323,000	152	4,630,000	157	4,921,000
Competing	43	1,248,000	36	1,097,000	31	972,000
Subtotal, individual	188	5,571,000	188	5,727,000	188	5,893,000
Total, research training	209	6,162,000	210	6,365,000	210	6,550,000
Research and development contracts	21	4,088,000	20	4,613,000	20	6,405,000
	FTEs		FTEs		FTEs	
Intramural research	257	30,590,000	263	31,471,000	261	32,084,000
Research management and support	85	9,873,000	88	10,152,000	88	10,540,000
Total	342	158,161,000	351	163,468,000	349	168,341,000
Clinical trials		(4,687,000)		(4,873,000)		(5,137,000)

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Summary of Changes

1995 Estimated budget authority	$163,468,000
1996 Estimated budget authority	168,341,000
Net Change	+4,873,000

Changes:	1995 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural:				
a. Annualization of January 1995 pay increase	---	$17,115,000	---	+$137,000
b. Within grade increases	---	17,115,000	---	+230,000
c. One more day of pay	---	17,115,000	---	+66,000
d. January 1996 pay increase	---	17,115,000	---	+282,000
e. Payment for centrally furnished services	---	6,704,000	---	+204,000
f. FTS decrease	---	125,000	---	-23,000
g. Service and Supply fund	---	4,540,000	---	+163,000
h. Increased cost of laboratory supplies, materials and other expenses	---	2,987,000	---	+90,000
Subtotal				+1,149,000
2. Research Management & Support:				
a. Annualization of January 1995 pay increase	---	5,304,000	---	+43,000
b. Within grade increases	---	5,304,000	---	+86,000
c. One more day of pay	---	5,304,000	---	+21,000
d. January 1996 pay increase	---	5,304,000	---	+89,000
e. FECF/unemployment comp	---	80,000	---	+3,000
f. Payment for centrally furnished services	---	1,880,000	---	+130,000
g. DHHS Working Capital Fund		215,000	---	-6,000
h. Service and Supply fund increase		645,000	---	+30,000
i. Increased cost of laboratory supplies, materials and other expenses		2,028,000	---	+58,000
Subtotal				+454,000

Summary of Changes--Continued

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	350	$58,874,000	-4	-$210,000
b. Competing	139	19,297,000	+4	+837,000
c. SBIR/STTR	17	2,646,000	--	+127,000
Total	506	80,817,000	--	+754,000
2. Research centers	27	20,734,000	--	+871,000
3. Other research	124	9,316,000	--	+270,000
4. Research training	210	6,365,000	--	+185,000
5. R&D contracts	20	4,613,000	--	+1,792,000
	FTE		FTE	
6. Intramural research	263	31,471,000	-2	-536,000
7. Research mgmt. & support	88	10,152,000	--	-66,000
Subtotal				+3,270,000
Total changes				+4,873,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment ceiling	351	349	-2
Full-time equivalent of overtime and holiday hours	2	2	---
Average ES salary	$109,880	$109,880	---
Average GM/GS grade	10	10	---
Average GM/GS salary	$46,400	$47,500	+$1,100
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	77,400	79,100	+1,700
Average salary of ungraded positions	25,000	25,600	+600
Personnel compensation:			
Full-time permanent	$11,958,000	$12,473,000	+$515,000
Other than full-time permanent	4,160,000	4,339,000	+179,000
Other personnel services	468,000	489,000	+21,000
Special personnel services	1,758,000	1,833,000	+75,000
Total personnel compensation	18,344,000	19,134,000	+790,000
Personnel benefits	4,127,000	4,301,000	+174,000
Benefits to former personnel	28,000	12,000	-16,000
Travel and transportation of persons	281,000	273,000	-8,000
Transportation of things	103,000	100,000	-3,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Rent, communications and utilities..	$915,000	$935,000	+20,000
Printing and reproduction...........	254,000	254,000	---
Other services:			
Consultant services............	271,000	272,000	+1,000
Other services.................	1,119,000	1,088,000	-31,000
Purchases from Govt. accounts..	14,573,000	15,017,000	+444,000
R&D contracts..................	2,102,000	3,740,000	+1,638,000
Supplies and materials..............	3,200,000	3,025,000	-175,000
Equipment...........................	842,000	798,000	-44,000
Grants, subsidies & contributions...	117,232,000	119,312,000	+2,080,000
Insurance claims and indemnities....	77,000	80,000	+3,000
Total, budget authority by object.	163,468,000	168,341,000	+4,873,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Administrative Costs

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)...	$11,958,000	$12,473,000	+$515,000
Other Than Full-Time Permanent (11.3)...........	4,160,000	4,339,000	+179,000
Other Personnel Compensation (11.5)........	468,000	489,000	+21,000
Special Personnel Service Payments (11.8)............	1,758,000	1,833,000	+75,000
Total Personnel Compensation (11.9)......	18,344,000	19,134,000	+790,000
Civilian Personnel Benefits (12.1).............	4,127,000	4,301,000	+174,000
Benefits to Former Personnel (13.0)............	28,000	12,000	-16,000
Travel (21.0).................	281,000	273,000	-8,000
Transportation of Things (22.0)................	103,000	100,000	-3,000
Communications, Utilities, & Miscellaneous Charges (23.3)	915,000	935,000	+20,000
Printing and Reproduction (24.0)..........	254,000	254,000	---
Consulting Services (25.1).....	271,000	272,000	+1,000
Other Services (25.2)..........	1,119,000	1,088,000	-31,000
Purchases from Government accounts (25.3)..............	11,379,000	12,580,000	+1,201,000
Supplies and Materials (26.0)..	3,200,000	3,025,000	-175,000
TOTAL......................	40,021,000	41,974,000	+1,953,000

National Institute of Dental Research

Significant Item in Senate Appropriations Committee Report

Item	Action Taken or to Be Taken
1995 Senate Report	
Temporomandibular joint disorder (TMJ)	
1. The Senate in its report 103-318, page 77, stated "The Committee is particularly concerned about the need for greater consensus regarding the number of people impacted by TMJ and on the most appropriate treatment modalities for TMJ."	1. Through an interagency task force, NIDR has commissioned experts to provide the best current information on the epidemiology and associated health care costs of the temporomandibular joint disorders. Future plans call for a technology assessment conference on diagnosis and treatment.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation........	Section 301	42§241	Indefinite	$157,103,000	Indefinite-	$161,791,000
National Institute of Dental Research...	Title IV, Part C, Section 453	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards.......	Section 487(d)	42§288	Such sums as necessary	6,365,000	Such sums as necessary	6,550,000
Total Budget Authority				163,468,000		168,341,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	$96,482,000	$116,275,000	$116,553,000	$117,945,000
1988	113,602,000	129,106,000 3/	131,559,000	126,297,000
1989	127,157,000 4/	127,315,000 5/	132,578,000	130,752,000
1990	131,527,000 6/	138,053,000	137,096,000	137,646,000
1990 Sequester				-1,897,000
1991	140,520,000	149,592,000 7/	151,057,000	148,918,000 8/
1991 Sequester				-2,000
1992	160,939,000	161,235,000	158,266,000	158,417,000 9/
1993	166,742,000	161,636,000	163,269,000	161,301,000 10/
1994	163,009,000	169,520,000	169,520,000	169,520,000
1995 11/	163,776,000	162,832,000	162,832,000	162,647,000
1996 11/	168,341,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread the funding among the Institutes, including $2,733,000 for the National Institute of Dental Research.

3/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

4/ The request excludes funds for AIDS research and education ($3,562,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $5,368,000 in NRSA training programs not considered.

6/ The request excludes funds for the National HIV Program ($4,269,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

7/ Excludes $5,893,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of $4,354,000.

9/ Excludes enacted administrative reductions of $1,753,000 and a rescission of $323,000.

10/ Excludes enacted administrative reductions of $1,968,000.

11/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

12/ Excludes enacted administrative reductions of $185,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTE	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Oral diseases and disorders research.		$112,578		$113,553		$117,681		$121,845		$125,717		+ $3,872
Intramural research....	277	28,768	274	29,180	257	30,590	263	31,471	261	32,084	-2	+ 613
Research management and support..........	84	9,400	88	10,008	85	9,860	88	10,152	88	10,540		+ 388
Total obligations....	361	150,746	362	152,741	342	158,131	351	163,468	349	168,341	-2	+ 4,873
Unobligated balance lapsing...............	--	17	--	26	--	30	--	---	--	---	--	---
Total, budget authority.	361	150,763	362	152,767	342	158,161	351	163,468	349	168,341	-2	+ 4,873

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Dental Research

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
342	$158,161,000	351	$163,468,000	349	$168,341,000	-2	+$4,873,000

General Statement

This document provides justification for the FY 1996 non-AIDS activities of the National Institute of Dental Research (NIDR). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research" (OAR).

The NIDR studies diseases and disorders that affect the teeth, mouth, jaws, and face. Early research showed that tooth decay and gum diseases were bacterial infections, paving the way for a variety of preventive measures in common use today. The result has been a dramatic improvement in the nation's oral health, with estimated annual savings close to $5 billion in dental care costs. Our goal now is to eradicate disease in individuals at highest risk, including many elderly Americans, while advancing knowledge about the normal growth and maintenance of the oral and facial tissues. Today our investigators are leaders in cell and molecular biology studies of disfiguring birth defects, chronic pain conditions, oral cancer, oral infections and immunity, bone and joint diseases, and in the development and testing of new diagnostics and biomaterials. We have shown that oral health cannot be separated from general health, and we have increased research on chronic diseases and treatments that can compromise oral health, including diabetes, osteoporosis, cancer, and AIDS.

Old and New Drugs to Treat Intractable Pain

The pain experienced in association with nerve damage (neuropathy) is considered among the most severe and intractable that patients can suffer. Recent studies indicate that such pain is mediated in part by a molecule called the N-methyl-D-aspartate (NMDA) receptor. A logical approach that NIDR investigators have adopted is to search for drugs that can block NMDA receptor activity. While several candidate drugs have been shown to be effective in patients, they have limited usefulness because of side effects, such as altered perception. More recently, investigators have discovered that dextromethorphan, a widely used cough suppressant, and its primary breakdown product, dextromethorphan, can also block the NMDA receptor. In addition, a drug used to treat Parkinson's disease, memantine, has been shown to reduce neuropathic pain in animals. Our scientists believe that safer and more specifically targeted NMDA receptor-blockers, combined with pain medications that work by other mechanisms, can provide the enhanced and sustained pain relief necessary to aid neuropathic pain patients. Following testing in animals, they plan to pursue clinical studies of combinations of drugs in neuropathic pain patients.

Fingerprinting Periodontal Bacteria

A number of different bacterial species can cause periodontal (gum) diseases, and within any given species, some bacterial strains are more virulent than others. In the past, distinguishing one strain from another has been problematic. Now, however, researchers have modified a DNA fingerprinting technique of the kind used in crime studies to identify which strains of bacteria are present at sites of infection in a patient's mouth. Not only can such knowledge aid clinicians in their treatment strategies, but the information can also be used to track how disease is transmitted from person to person. For example, researchers have identified several strains of *Actinobacillus actinomycetemcomitans*, a bacterial species associated with a severe familial form of periodontal disease seen in young people. In six out of seven families studied, the husband and wife harbored different strains of *A.a*., but the children carried strains identical to those found in one of the parents--suggesting that the bacteria were transmitted from parent to child.

In other research, staff scientists are conducting a genome-wide search for the gene or genes involved in early onset periodontitis. They are collaborating with investigators at Virginia Commonwealth University who have located affected families.

Minority Centers

NIDR is funding several 5-year awards for Regional Research Centers for Minority Oral Health in FY 1995. Over the past 3 years, each of six minority dental schools or dental schools serving predominantly minority populations has worked in collaboration with one or more research-oriented institutions, using planning grant awards to initiate research studies and faculty enhancement programs. The planning period was designed to enable the schools to compete for full-scale 5-year center awards. The minority schools, located in Los Angeles, San Antonio, Washington, Newark, Nashville, and New York City, have conducted a wide range of research that includes studies of diabetes and oral health in Mexican-Americans; susceptibility to dental caries; the role of diet and lifestyle in minority oral health; comparisons of Hispanic mother-daughter pairs in relation to periodontal disease; and risk factors for oral cancer. The 1994 meeting of the Center Directors included scientific presentations by an emerging group of young minority investigators and emphasized the desire of the regional centers to share data and collaborate through an information network and regular meetings.

Oral Health Information Clearinghouse

January 1994 saw the formal opening of an NIDR National Oral Health Information Clearinghouse (NOHIC) designed to serve as a resource for care providers and "special care" patients--individuals with systemic diseases or disorders that directly or indirectly affect their oral health. Inquiries during the first few months of operation rose dramatically with over 4,000 requests being received by phone, mail, fax, and Internet by year's end. In addition to developing a database of existing information and education resources (which is included as a subfile of the Combined Health Information Database, a national online database) NOHIC is also developing original materials. In the first year, these included packets of information on temporomandibular disorders for patients and professionals, and a slide program for professionals on the periodontal complications of diabetes. In addition NOHIC distributes brochures and periodic bulletins about the Clearinghouse itself. A 13-member Coordinating Panel representing special care patients, dental professionals, and the research and health education communities meets annually to provide oversight and advice to the Clearinghouse.

The President's appropriation request of $168,341,000 represents current law requirements. No proposed law amounts are included. Funding for the NIDR during the last 5 years has been as follows:

	Amount	FTE
FY 1991	$142,488,000	335
FY 1992	150,763,000	361
FY 1993	152,767,000	362
FY 1994	158,161,000	342
FY 1995	163,468,000	351

Purpose and Method of Operation

Extramural research and training are supported through seven program areas; and funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at eight laboratories, including a dental clinic and pain research unit located in the NIH Clinical Center and a Division of Epidemiology and Oral Disease Prevention. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

Overall Budget Policy

The FY 1996 budget request for NIDR is $168,341,000, an increase of $4,873,000 or 3.0 percent over the comparable FY 1995 level of $163,468,000.

At the request level, the Institute will support 346 noncompeting research project grants at $57,303,000 and 143 new and competing renewal grants at $20,134,000, compared to 350 and 139, respectively, in FY 1995. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a 4-percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment. The average cost of competing awards will be within BRDPI limits over the FY 1995 estimated average cost.

A total of 27 research centers will be supported at a cost of $21,605,000 in FY 1996, compared to the $20,734,000 for the same number of centers in FY 1995.

The other research grant category will be supported in FY 1996 at a total of $9,586,000 for 124 awards. The Institute will fund approximately 112 research career positions at $8,317,000; the Minority Biomedical Research Support Program will receive $202,000; and $1,067,000 will be available for other research related awards such as conference grants, small instrumentation grants, and scientific evaluation grants.

A total of $6,550,000 will support approximately 210 full-time training positions (FTTPs) in the National Research Service Awards program in FY 1996, compared to $6,365,000 for the same number of FTTPs in FY 1995. The average cost per trainee is increased by 2.9 percent.

Research and development contracts will be supported at $6,405,000, compared to $4,613,000 in FY 1995.

Support for intramural research, including the Institute's Division of Epidemiology and Oral Disease Prevention, will be $32,084,000, an increase of $613,000 over FY 1995. Research management and support activities will be funded at $10,540,000, an increase of $388,000 over FY 1995. The President's Budget request includes provisions for reducing full-time equivalent (FTE) positions by 2 FTEs in FY 1996. The NIDR request also incorporates the requisite provisions for administrative cost reductions in FY 1996.

National Institute of Dental Research

Extramural Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$117,698,000	$121,845,000	$125,717,000	+$3,872,000

Research is focused on the causes, prevention, diagnosis, and treatment of diseases and abnormal conditions that affect the teeth, mouth, and jaws.

Funding for Oral Diseases and Disorders Research during the last 5 years has been as follows:

	Amount
FY 1991	$106,378,000
FY 1992	112,578,000
FY 1993	113,555,000
FY 1994	117,698,000
FY 1995	121,845,000

Rationale for the Budget Request

The FY 1996 budget request for this activity is $125,717,000, an increase of 3.2 percent over the FY 1995 estimate of $121,845,000. The following are a few examples of research activities to be funded in Oral Diseases and Disorders Research.

Progress on Jaw Pain

The jaw (temporomandibular) joint is considered the most complex joint in the body, and pain and dysfunction associated with jaw tissue and/or the surrounding muscles has been a source of unremitting problems for a large and predominantly female patient population. In particular, a number of women who have had surgery to replace parts of the jaw joint with a plastic prosthesis have experienced major complications as a result of the breakdown of the plastic and release of particles into the tissue.

Our investigators have long advocated conservative--non-invasive procedures in the treatment of temporomandibular disorders (TMDs)--seeing a need for better understanding of conditions that can give rise to jaw problems as well as improved diagnostics and treatments aimed at preventing acute jaw pain and dysfunction problems from becoming chronic. To address the issues, the Institute sponsored the first World Workshop on TMDs and Related Pain Conditions in April 1994. The interdisciplinary workshop, co-sponsored with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the NIH Office of Research on Women's Health, and the Agency for Health Care Policy and Research, brought together over 100 scientists as well as representatives of patient groups and Congress for a review of the state of the science and the development of research recommendations.

The workshop laid the groundwork for research that can be pursued immediately, including exploring the question of gender; the roles and interactions of the nervous, endocrine, and immune systems in response to tissue injury, inflammation, and repair; the need for model systems; and increased molecular biology studies of the mechanisms underlying deep muscle and joint pain.

Two other meetings in 1994 underscored the commitment of NIDR to move rapidly to resolve issues with regard to TMDs: one meeting focused on the biobehavioral aspects of pain research, and the second addressed the issue of joint implants specifically. In this regard, NIDR has issued a Request for Proposals to study the biochemical, molecular, and cellular responses associated with failed plastic jaw implants.

Health Effects of Mercury-Containing Amalgams

In our continuing efforts regarding the health effects of amalgams, NIDR has been fortunate in being able to collaborate with the U.S. Air Force in a long-term study of Vietnam veterans. Extensive medical and dental records are available for the veterans who are seen and evaluated periodically. NIDR added a dental examination to quantify the number of amalgam fillings and to collect blood and urine samples. The examinations have now been completed, and our investigators have begun analyzing the data to determine if there is any correlation between amalgam exposure over time and changes in neurological, immunological, or kidney function. We are also working closely with the National Institute of Environmental Health Sciences and with international experts in exploring issues relating to total body burden of mercury because of the presence of the metal in the food chain and in the atmosphere.

Research on alternatives to amalgam is also proceeding. We are currently working with private industry in the development of a mercury-free metal filling that is undergoing further testing for safety and durability. Research to develop stronger composites--plastic materials that can be color matched to the natural teeth--is also under way.

Finding Genes for Disfiguring Birth Defects

The rapid development and automation of genetic and molecular techniques over the decade has been a major incentive to researchers studying craniofacial birth defects, among the most common serious afflictions of newborns. Success last year in identifying a gene associated with craniosynostosis--the term to describe a spectrum of malformations due to premature closure of skull bones--has led to the establishment of a new Center for Craniofacial Development and Disorders at the John Hopkins School of Medicine. The goal of the center is to identify the genes and the timing of events that govern normal skull development and to determine what goes wrong in craniosynostosis, which occurs in 1 out of 3,000 newborns. Since the gene that was identified in the earlier study turned out to be ancient--analogous to genes found in fruit flies, sea urchins, and other primitive life forms--the investigators' research is expected to contribute to a basic understanding of one of the riddles of life: how a single cell develops into the multiple organs and distinct form that characterizes the mature animal.

NIDR supports other interdisciplinary teams in developmental biology, including a center at the University of Iowa that is making use of that state's registry to locate families with infants born with clefting syndromes, and a center at the University of Southern California which has been a prime mover in research on the development of dental tissues. These researchers have perfected methods enabling them to observe tooth development in tissue culture.

National Institute of Dental Research

Intramural Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1996 Authorization: Indefinite

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
257	$30,590,000	263	$31,471,000	261	$32,084,000	-2	+$613,000

Intramural research at the NIDR is conducted in eight laboratories and branches. A dental clinic and a pain research unit are maintained in the NIH Clinical Center to conduct research and diagnostics for patients. The Institute's intramural research budget activity also includes a Division of Epidemiology and Oral Disease Prevention.

Funding for NIDR intramural research during the last 5 years has been as follows:

	Amount	FTEs
FY 1991	$26,423,000	262
FY 1992	28,785,000	277
FY 1993	29,193,000	274
FY 1994	30,590,000	257
FY 1995	31,471,000	263

Rationale for the Budget Request

The FY 1996 budget request for this activity is $32,084,000, an increase of $613,000 over the FY 1995 comparable amount. The following are examples of research activities conducted in the NIDR intramural research program.

New Bone Clinic

NIDR has initiated the first protocol in its newly established Bone Clinic in the NIH Clinical Center. The study is based on findings that cells located in bone marrow, so called "stromal" cells, have the potential to develop into bone-forming cells. The investigators will harvest marrow stromal cells from volunteers and see if the cells can generate new bone when implanted in a strain of animals lacking an immune system (so that the grafts will not be rejected). If successful, the next step will be to move to treat patients with bony defects. These can occur in cases of trauma, disease, and toothlessness (where there is resorption of the jaw bone).

Future protocols in the Bone Clinic will involve our investigators in collaborations with other NIH components as well as with grantees and the private sector. In taking this step NIDR is capitalizing on its major investment in research on bones and teeth over the years--research that has led to the identification of dozens of genes and proteins involved in bone growth and turnover; the isolation and mapping of genes associated with genetic and chromosomal abnormalities; new methods that allow long-term culture of bone cells in laboratory dishes; and the discovery of families of bone growth factors that are now being synthesized commercially by biotechnology companies. The movement from basic to clinical research reflects the Institute's concerted effort to respond to the increasing prevalence of bone and joint diseases as the population ages. As part of this effort, we have alerted the academic community through Program Announcements inviting submission of grant applications in the area of osteoporosis in relation to oral bone loss and in wound healing.

Matrix Metalloproteinases--Agents of Environmental Change

Studies of how teeth and bones are formed have led to major discoveries about so-called "extracellular matrices." These are mixtures of connective tissue proteins, such as collagens, that are deposited outside bone- and tooth-forming cells and used by the cells in making hard tissues. Other kinds of extracellular matrices are found throughout the body's tissues, surrounding nerves and blood vessels, and underlying the skin. Scientists now know that cell-matrix interactions play a vital role in embryonic development, in the growth and differentiation of cells, and in tissue maintenance and repair.

Cells also produce certain enzymes, called matrix metalloproteinases (MMPs), that can degrade extracellular matrix. In this way the enzymes enable the cell to change its environment and to move and migrate--as happens in embryonic development. But the enzymes are also produced in certain inflammatory diseases such as periodontal disease, where they contribute to tissue destruction by breaking down the connective tissue and bone that supports the teeth. To further pursue this area of research, NIDR has established a new intramural research unit that will focus on MMPs.

Schoolchildren's Survey

Staff of the Institute's Division of Epidemiology and Oral Disease Prevention have completed plans for the next major national survey of the oral health of schoolchildren between 5 and 17 years old. The survey, which will be conducted during the 1996-97 school year, will provide the database needed to evaluate shorter- and longer-term trends in caries, juvenile periodontal disease, and tobacco-related soft tissue lesions in U.S. schoolchildren. An oversampling of minority children will be included.

National Institute of Dental Research

Research Management and Support

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1996 Authorization: Indefinite

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
85	$9,873,000	88	$10,152,000	88	$10,540,000	--	+$388,000

This activity provides the leadership and management direction of the entire Institute in addition to the administrative management and scientific direction in the review, award, and monitoring of all extramural awards. Associated with this activity is the immediate Office of the Director and the Institute's program and administrative staff.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTEs
FY 1991	$9,687,000	73
FY 1992	9,400,000	84
FY 1993	10,019,000	88
FY 1994	9,873,000	85
FY 1995	10,152,000	88

Rationale for the Budget Request

The FY 1996 budget request for research management and support (RMS) is $10,540,000, an increase of $388,000 over the FY 1995 level. The RMS activity will continue to provide leadership, program guidance, planning and evaluation, and overall administration for the programs and information directed to scientists, dental practitioners, and the public, in addition to continuing to administer, manage, and review the Institute's grant and contract programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Detail of Full-time Equivalent Employment (FTE)

	1994 Actual Usage	1995 Ceiling	1996 Ceiling
Office of the Director..........	9	10	10
Office of Administrative Management....................	17	18	18
Office of Planning, Evaluation, and Communications............	22	22	22
Division of Extramural Research.	37	38	38
Division of Epidemiology and Oral Disease Prevention.......	43	44	44
Division of Intramural Research.	214	219	217
Total, NIDR................	342	351	349

Average GS/GM Grade

1990...............	9.8
1991...............	9.7
1992...............	9.6
1993...............	9.8
1994...............	10.0
1995...............	10.0
1996...............	10.0

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

14

National Institute of Dental Research

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-6	--	1	1
ES-5	--	1	1
ES-4	4	3	3
Subtotal	4	5	5
Total ES Salary	$429,200	$549,400	$549,400
GS/GM-15	24	24	24
GS/GM-14	32	31	31
GS-GM-13	20	25	25
GS-12	26	27	27
GS-11	24	24	24
GS-10	1	1	1
GS-9	17	19	19
GS-8	11	12	12
GS-7	26	28	28
GS-6	21	21	21
GS-5	12	13	13
GS-4	5	5	5
GS-3	1	1	1
Subtotal	220	231	231
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	15	15	15
Senior Grade	4	4	4
Full Grade	1	1	1
Senior Assistant Grade	4	4	4
Subtotal	24	24	24
Ungraded	84	89	89
Total permanent positions	231	242	242
Total positions, end-of-year	332	349	349
Total full-time equivalent (FTE) employment, end-of-year	342	351	349
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$107,300	$109,880	$109,880
Average GS/GM grade	10	10	10
Average GS/GM salary	$44,995	$46,400	$47,500

TUESDAY, MARCH 21, 1995.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

DR. MARVIN CASSMAN, ACTING DIRECTOR
DR. W. SUE SHAFER, ASSOCIATE DIRECTOR FOR EXTRAMURAL ACTIVITIES
MARTHA PINE, EXECUTIVE OFFICER
G. EARL HODGKINS, FINANCIAL MANAGEMENT OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. The subcommittee will come to order.

I've already testified myself before two other subcommittees of Appropriations this morning, and I do apologize to all of you for delaying the start of this hearing.

We're pleased to have Dr. Marvin Cassman, the Acting Director of the National Institute of General Medical Sciences, here to testify this morning. Dr. Cassman, why don't you introduce the people at the table with you, and then proceed in any way you wish?

INTRODUCTION OF WITNESSES

Dr. CASSMAN. Thank you, Mr. Porter.

To my far left is Dr. Sue Shafer, our Associate Director for Extramural Activities. Next to her is Earl Hodgkins, the Financial Management Officer of NIGMS. And on my immediate left is Martha Pine, the Executive Officer. And Mr. Williams I think you already know.

Mr. PORTER. He gets introduced every year. [Laughter.]

OPENING STATEMENT

Dr. CASSMAN. Mr. Chairman, good morning. I'm pleased to present to you the programs of the National Institute of General Medical Sciences, the NIGMS. NIGMS supports basic biomedical research that increases our understanding of life processes and lays the foundation for advances in the diagnosis, treatment and prevention of disease. NIGMS-supported research also provides the concepts, tools and techniques that are applied and commercialized by the pharmaceutical industry and by the increasing number of other industries that use the approaches of modern biology.

In recognition of the importance of the basic research that NIGMS supports, a significant number of the Nobel Prizes in biology and chemistry have gone to our grantees. I counted them up last night; I think there are about 55 in total.

[CLERK'S NOTE.—Subsequent to the hearing, NIGMS corrected the number of grantees receiving Nobel Prizes to 63.]

In 1994, these included Dr. Alfred Gilman of the University of Texas Southwestern Medical Center at Dallas and Dr. George Olah of the University of Southern California. Dr. Gilman's research is right in the middle of one of the most exciting areas of modern biology, the communications system that regulates cellular activity. Aberrations in this system underlie a variety of disease states, from cancer to cholera. Dr. Olah, a synthetic chemist, has studied molecules that are involved in natural and synthetic processes. These have led to reagents and methods that are used today in the production of a wide variety of materials, from pharmaceuticals to gasoline.

A good example of how NIGMS-supported research is being applied to improve health and benefit the economy is found in the area of pharmaceuticals, where grantees are generating knowledge that leads to the discovery and design of new therapeutic drugs. And these new directions come from many different areas.

One is structure-based drug design, which has also been identified as an area for special emphasis in the NIH budget. Structure-based drug design targets proteins that we can identify as key elements involved in a disease. For example, earlier in these hearings, both Dr. Varmus and Dr. Fauci referred to the protease found in the human immunodeficiency virus, the HIV virus that causes AIDS. By knowing the structure of the protease, it was possible to design small molecules that could specifically bind and inactivate it. This approach has the potential of bypassing the time-consuming screening processes that are at the heart of much of the drug development currently performed.

Other researchers are examining how existing and potential therapeutic compounds work in the body—how much of a compound reaches the target site; how long it stays at that site; how the compound is changed by the body; and what effect it has. It's sometimes thought that if you can demonstrate an activity in a test tube, that means you have a drug, and that's simply not true. Going from an active molecule in a test tube to a drug is a long process, and all of these things that happen within the body when you introduce a new compound are one of the things that is essential to understand.

The results of this research indicate ways that compounds could be modified to enhance their activity and reduce their side effects. This approach was used to explain how an antihistamine, for example, interacts with certain other drugs to produce dangerous changes in heart rhythms, and it has pointed the way to how the safety of some antihistamines could be improved.

Other grantees are using a combination of genetic and chemical methods to develop potential therapeutic compounds. One system recently developed mimics evolution by putting molecules through repeated cycles of mutation, followed by the selection of variants with certain properties. This approach could shorten the time required to come up with viable drug candidates from years to months. Using this system, a company took less than four months to generate a library of molecules, screen them for the ability to bind to and block a hormone that promotes cell growth, and then move several of the compounds into animal tests as a potential treatment for cancer and other conditions.

I would hope that it's not surprising that we can give you many examples of how the research that we support contributes to the health of the U.S. public. After all, that's what we're supposed to do. What may be more of a surprise is how broad an impact this research has.

Consider the powerful tool known as the polymerase chain reaction, or PCR, which has already brought the discoverer the Nobel Prize. Using PCR, scientists can replicate a single molecule of DNA, of a variety of origins, up to one billion times within a few hours. Both the conceptual and methodological foundations of PCR were dependent on research supported by the NIGMS as depicted in the chart you have in front of you and the chart that's on this easel.

There are a few points that I would like to make about this actually rather complicated looking chart. First, there are many independent lines of research that contributed to the development of the final PCR reaction. These lines of research were conducted not because people wanted to find out how to generate such a reaction, but because they wanted to develop a knowledge of the fundamental aspects of biological systems. And in the process, all these contributed ultimately to understanding and developing the PCR reaction.

Now, the contributions of the National Institute of General Medical Sciences are blocked out in blue. There are just a few points I want to make about this. First of all, we're clearly not the only player in the development of PCR. Other parts of the NIH contributed, as did other parts of the Federal Government, the National Science Foundation included, as well as industry and foreign institutions. The National Institute of General Medical Sciences' contribution to this development was, I think, the major contribution, but we take pride in being part of a larger effort.

The second point I want to make is that our work comes early in the process. This isn't surprising. Our investigators focus on a fundamental understanding of biological systems, which can lead to different outcomes. As one approaches the point of application, we at NIGMS have less of a role. PCR has become a pivotal technique for both basic research and industrial research. There are now 1,300 biotech companies, approximately, with about $10,000,000,000 in revenues, and roughly 100,000 employees. And I would guess that every one of these companies uses PCR in one form or another, and several of them, many of them, actually, exist because of the development of PCR.

There are a variety of applications of broad scope. The biotechnology industry uses PCR for gene discovery. There is forensics, paternity suits among others; in medicine, disease testing and prenatal testing; in agriculture, it's used for plant and animal breeding, and microbial testing of food products; and of course, it is used in a wide variety of basic research efforts.

Now, as the PCR chart makes clear, the fundamental discoveries reported by NIGMS often have unexpected outcomes, including economic benefit. Recently, a company has announced, a small biotech company—well, actually not so small, a biotech company has announced that it had developed a commercially competitive new way to produce the dye indigo using biological processes, not chemical ones. Indigo, which is used to make denim, is the world's largest selling dye.

Well, you can reasonably ask, what does an organization that is devoted to biomedical research have to do with the production of a dye? The answer is that the foundation of this new approach was laid by a long-time NIGMS investigator, Dr. David Gibson, who is now at the University of Iowa. In 1983, Dr. Gibson was at the University of Texas, at Austin, where he was studying the enzymes involved in the way the bacterium *E. coli* eats hydrocarbons. To his surprise, in the course of one of his studies, the bacterial cells turned bright blue. When he looked at the reason for this, he found that he had produced indigo. This was not his intention, but it happened in the course of the research.

Although Dr. Gibson and his colleagues determined the pathway and published in 1983–84 the papers describing the pathway that led to the production of indigo in these cells, turning the discovery into a commercial process has taken many years of work, much of which has involved the efforts of a collaborator of Dr. Gibson's in those 1983 studies. I'd like to point out that this is probably the way technology transfer really works. Most of the time, you don't transfer technologies by moving ideas; you generally do it by moving the people who have the ideas.

The new biosynthetic process will compete for a share of the $200,000,000 worldwide indigo market. Apart from its direct economic consequences, the biosynthetic approach has other important benefits. The current chemical synthesis of indigo, which dates from 1883, uses hazardous agents, including cyanide, and generates highly toxic byproducts. The new process uses recombinant DNA technology to synthesize indigo biologically. This biosynthetic approach is environmentally more benign and uses a renewable resource, glucose, rather than the petroleum-based hydrocarbons that are the starting point in the chemical synthesis of indigo.

This exciting industrial application emerged from a discovery made by an investigator who was looking at some fundamental properties of living organisms. Additionally, the ability to turn the discovery into a commercial product was the result of recombinant DNA technology, much of which came from NIGMS-supported research, and which has contributed broadly to the biotechnology industry.

There are a variety of other examples of this type I can give. I'll just mention one briefly, the production of food additives used in animal feed. Until fairly recently, this market was dominated by the Japanese, using traditional fermentation methods. But because of major, largely academic advances in biotechnology, there are a variety of U.S. companies that are beginning to use recombinant organisms to develop these food additives.

Now, after saying all this about industrial development, I would like to make it quite clear that our primary function is not to support industry. We support basic research in biology and chemistry for the purpose of understanding and addressing the issues of health and disease. And there are many examples of NIGMS contributions to understanding health and disease in such rapidly developing areas as the regulation of cellular activity, including the control of cell growth and division, which can reveal what happens when these processes go awry and result in birth defects and diseases such as cancer.

Another area of rapid growth now is targeted gene replacement, which has already given clues to the cause of salt-sensitive hypertension. We make our contributions to the fundamental understanding of biological systems, which becomes of use in ways that we could never anticipate, although we could have been quite certain that such unanticipated consequences would emerge. We just couldn't have said what they would be.

The NIGMS' research programs are complemented by training programs that produce scientists who are prepared to conduct the interdisciplinary research required in the future. Our goal is to provide a high quality training environment to outstanding students who will meet the needs of industry and academia.

This approach is consistent with a recommendation made in a 1988 OTA report that, "Rather than trying to direct market forces, policy makers should seek to prepare a cadre of versatile scientists and engineers for research and teaching careers, to invest in an educational system that creates a reservoir of flexible talent for the work force, and to ensure opportunities for the participation of all groups in science and engineering."

This is precisely what the NIGMS programs have attempted to do and I believe do very well. We also believe that we should ensure opportunities for the participation of all groups in the biomedical sciences. And so we are continuing our efforts to promote and encourage the representation of minority groups in biomedical research, through both targeted research and training programs.

We have recently been engaged in intensive efforts to develop strategies for the future in these programs, to develop new approaches and optimize our resources. These include efforts to increase retention and graduation rates of minorities in the sciences, and attempts to increase the number of minority M.D.s who become involved in research.

Mr. Chairman, the fiscal year 1996 budget request for the National Institute of General Medical Sciences is $907,674,000. And I'd be pleased to answer any questions that you may have.

Thank you.

[The prepared statement and biography of Dr. Marvin Cassman follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Acting Director
National Institute of General Medical Sciences

Mr. Chairman and Members of the Committee, good morning. I am pleased to present to you the programs, progress, and plans of the National Institute of General Medical Sciences (NIGMS).

NIGMS supports basic biomedical research that increases our understand-ing of life processes and lays the foundation for advances in the diagnosis, treatment, and prevention of disease. NIGMS-supported research also provides concepts, tools, and techniques that are applied and commercialized by the pharmaceutical industry and by the increasing number of other industries that use the approaches of modern biology, thus fueling their growth and helping to maintain our Nation's position as a world leader in these sectors.

In recognition of the importance of the basic research NIGMS supports, a significant number of the Nobel Prizes in biology and chemistry have gone to our grantees. In 1994, these included Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center at Dallas and Dr. George A. Olah of the University of Southern California. Dr. Gilman's research has clarified key steps in the communication system that regulates cellular activity. Aberrations in this system underlie a variety of disease states, from cancer to cholera. Dr. Olah's studies of molecules involved in natural and synthetic chemical processes led to reagents and methods that are used today in the production of a wide variety of materials, from pharmaceuticals to gasoline.

Drug Discovery and Design

A good example of how NIGMS-supported research is being applied to im-prove health and benefit the economy is found in the area of pharmaceuticals, where grantees are generating knowledge that leads to the discovery and design of new therapeutic drugs. This knowledge comes from many directions.

One approach involves determining the structures and functions of biologically important molecules. This information helps scientists design chemical compounds that can bind to the molecules with great precision and either block or enhance their activity.

Another approach focuses on finding ways to synthesize desired molecules in the most efficient manner and to modify molecules to optimize their activity. The chemical techniques used in this approach also have applications outside the pharmaceutical arena. For instance, a grantee's method to synthesize large quantities of molecules in a single spatial orientation, which was developed to improve the purity of synthetic drugs, has also been used to make the chemical attractant for gypsy moth traps and has been licensed by such companies as Hoechst and ARCO for industrial purposes. Most important, though, is that this and similar techniques offer an opportunity for real clinical benefit by making it feasible to eliminate unwanted--and possibly harmful--components of drugs.

A third research area encompasses how existing and potential therapeutic compounds work in the body--how much of a compound reaches the target site and how long it stays at that site, how the compound is changed by the body, and what effects the compound has. The results of this research indicate ways that compounds could be modified to enhance their activity and reduce their side effects. This approach was used to explain why the antihistamine Seldane® interacts with certain other drugs to produce dangerous changes in heart rhythms, and it has pointed the way to how the safety of Seldane® could be improved.

Other grantees are using a combination of genetic and chemical methods to discover potential therapeutic compounds. One system mimics evolution by putting molecules through repeated cycles of mutation followed by the selec-tion of variants with certain properties. This strategy does not require the design and synthesis of new compounds or the screening of existing compounds--two common, but very labor-intensive, methods of drug discovery. Thus, the system could shorten the time required to come up with viable drug candidates from years to months. Using the system, a Colorado company called NeXagen took less than 4 months to generate a library of molecules; screen them for the ability to bind to and block a hormone that promotes cell growth; and move several of the compounds into animal tests as potential treatments for cancer and other conditions.

Powerful Tool

I would hope that it is not surprising that we can give you many examples of how the research we support contributes to the health of the U.S. public. After all, that is what we are supposed to do. What may be more of a surprise is how broad an impact this research has.

Consider the powerful tool known as the polymerase chain reaction, or PCR. Using PCR, scientists can amplify a single molecule of DNA--of bacterial, viral, plant, or animal origin--up to 100 billion times within a few hours. Both the conceptual and methodological foundations of PCR were dependent on research supported by NIGMS, as depicted in the attached chart. The chart shows how many lines of research were required to ultimately result in the PCR reaction. There are a few points that I would like to make. First, you will note that NIGMS is by no means the only player in the development of PCR. There were many contributors, including other parts of NIH; other parts of the Federal Government, such as NSF; as well as industry and foreign institutions. We are the major contributor, but we also pride ourselves on being part of a larger effort. The second point is that the majority of our contributions came early in the process. This is not surprising, since our investigators focus primarily on attempting to understand the underlying principles of biological systems, which can lead to many different outcomes. In this case, one of the outcomes of the fundamental studies was the PCR process. As one gets closer to the application of these results, we become less involved.

PCR has become a pivotal technique in basic research as well as in a large number of industrial applications. There are currently more than 1,300 biotechnology companies in the United States, accounting for $10 billion in revenues and employing 100,000 people. Virtually all of these companies use PCR for some aspect of their research, product development, or services, and several dozen companies exist solely as a consequence of PCR. Among the companies that depend heavily on PCR are those involved in genetic and infectious disease testing, forensic testing, plant and animal breeding and disease testing, and food product safety testing. The use of PCR by these companies has, in turn, spawned the development and sale of chemicals, instruments, and other products that support PCR. Furthermore, PCR is an essential technology in the Human Genome Project, which holds promise for stimulating rapid growth in the medical diagnostics industry and, eventually, for the development of new pharmaceuticals and for gene therapy.

Economic Impacts

As the PCR chart makes clear, the fundamental discoveries supported by NIGMS often have unexpected outcomes. Another example of such an outcome involves the synthesis of small chemicals for industrial purposes. Recently, a Rochester, New York biotech company named Genencor International announced that it had developed a commercially competitive new way to produce the dye indigo using biological processes, not chemical ones. Indigo, which is used to make denim, is the world's largest-selling dye.

The foundation of the new approach was laid by a long-time NIGMS investigator, Dr. David Gibson, who is now at the University of Iowa. In 1983, Dr. Gibson was at the University of Texas at Austin, where he studied the enzymes involved in the way the bacterium E. coli eats hydrocarbons. To his surprise, in the course of one of his studies, the bacterial cells turned bright blue. This was due to the production of indigo. Although Dr. Gibson and his colleagues determined the pathway by which this unusual event occurred, turning the discovery into a commercial process has taken many years of work, much of which has involved the efforts of a collaborator of Dr. Gibson's in the 1983 studies.

The new, biosynthetic process will compete for a share of the $200 million worldwide indigo market. Currently, four companies control this market, three of which are non-U.S. Apart from its direct economic consequences, the biosynthetic approach has other important benefits. The current chemical synthesis of indigo, which dates from 1883, uses hazardous reagents (including cyanide) and generates highly toxic byproducts. The new process uses recombinant DNA technology to synthesize indigo biologically. This biosynthetic approach is environmentally more benign, and uses a renewable resource, glucose, as its starting point, rather than the petroleum-based hydrocarbons used in the chemical synthesis of indigo.

This exciting industrial application emerged from a discovery made by an investigator who was looking at some fundamental properties of living organisms. Additionally, the ability to turn the discovery into a commercial product was a result of recombinant DNA technology, much of which came from NIGMS-supported research and which has contributed broadly to the biotechnology industry.

Another example of small molecule production of economic importance that has emerged from the development of recombinant DNA techniques is the production by recombinant organisms of food additives used in animal feed. Until fairly recently, this market was dominated by the Japanese, utilizing traditional fermentation techniques. American firms are now making significant inroads into the Japanese share of the market by using genetically modified organisms that can produce the compounds in higher yield than the traditional methods. I should point out that many of the companies involved in the production of these animal feeds have no tradition of R&D at all. They are totally dependent on largely academic research for the new concepts that they then apply.

Now, I would like to make it quite clear that our primary function is not to support industrial development. We support basic research in biology and chemistry for the purpose of addressing the issues of health and disease. However, the fundamental understanding of biological systems that we help promote has become of use in ways that we could never anticipate, although, since that is the nature of basic research, we could have been quite certain that such unanticipated consequences would emerge. We just couldn't have said which they would be.

Areas of Opportunity

As is the case in so many areas of science today, there is an unprecedented wealth of opportunities in the fields of basic research that NIGMS supports. Advances in these areas are likely to have a major impact on progress in biomedical science and the treatment of disease. Among the areas are the study of the structures of cell membrane proteins, which are frequently the targets of therapeutic drugs; protein and metabolic engineering, which could make it easier to produce molecules for therapeutic or synthetic purposes; and deeper understanding of the regulation of cellular activities, including cell-to-cell communication and the cycle of cell growth and division, which could reveal what happens when these processes go awry and lead to birth defects and diseases such as cancer.

Preparing the Scientists of the Future

NIGMS' research programs are complemented by training activities that produce scientists who are prepared to conduct the interdisciplinary research that is increasingly common today and that is expected to be even more important in the future. Our goal is to provide a high-quality training environment to outstanding students who will meet the needs of industry and academia. This approach is in keeping with the recommendation, made in a 1988 report by the Office of Technology Assessment (OTA), that "policymakers should seek to prepare a cadre of versatile scientists and engineers for research and teaching careers, invest in an educational system that creates a reservoir of flexible talent for the work force, and ensure opportunities for the participation of all groups in science and engineering."

NIGMS has special initiatives in areas that have shortages of well-trained scientists. These areas include biotechnology and the interface between the fields of chemistry and biology. Another special activity is the Medical Scientist Training Program, which supports students who plan to combine basic research and clinical investigation. These individuals are exceptionally well-qualified to translate basic research findings into medical advances.

Minorities in Science

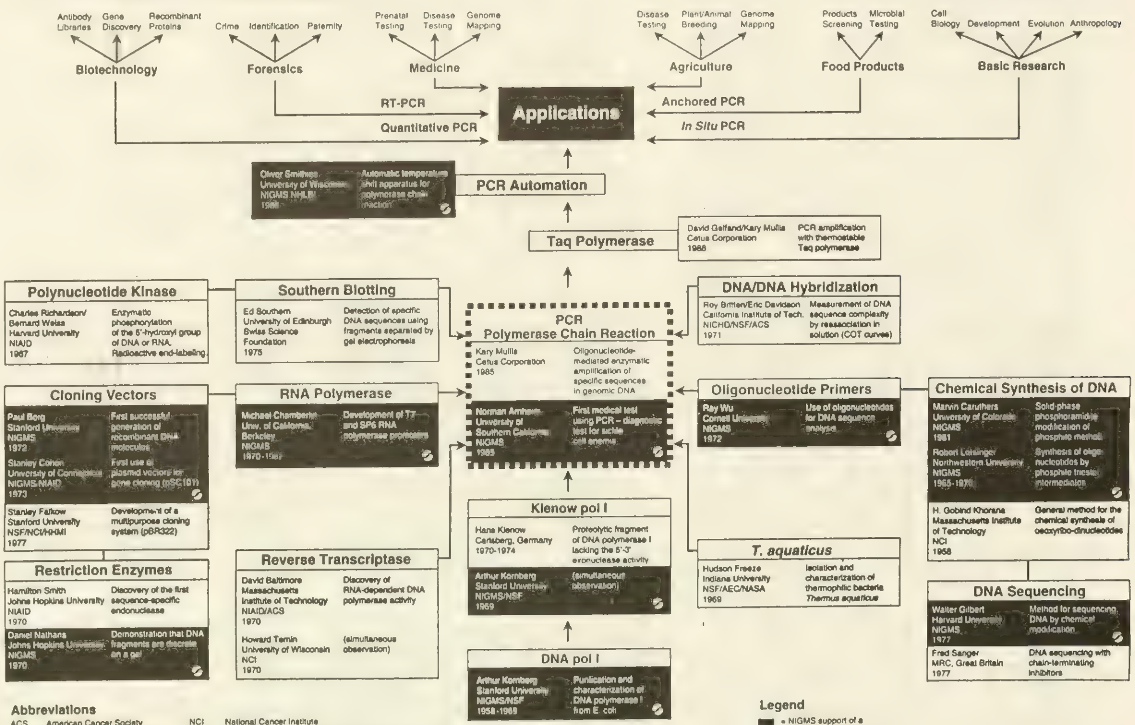
In regard to the OTA recommendation that we "ensure opportunities for the participation of all groups in science and engineering," one of the NIGMS divisions is devoted to increasing the representation of scientists from minority groups in biomedical research. The division sponsors a variety of research and training programs, some targeted to students and faculty at institutions with substantial minority enrollments and others targeted to minority students at any academic institution.

The division has recently been engaged in intensive efforts to develop strategies for the future. Among the areas it plans to emphasize are: activities to expand the base of institutions and organizations that are helping to increase the representation of minorities in biomedical research; efforts to increase retention rates and graduation rates of minorities majoring in the sciences; and efforts to increase the number of minority M.D.'s who become involved in research.

Mr. Chairman, the fiscal year 1996 budget request for the National Institute of General Medical Sciences is $907,674,000. I would be pleased to answer any questions that you might have.

Basic Re‸‸rch Leading to PCR and its Applications

Natio‸‸ ‸stitute of
General Medical Sciences



Polynucleotide Kinase
Charles Richardson/ Bernard Weiss, Harvard University, NIAID, 1967 — Enzymatic phosphorylation of the 5'-hydroxyl group of DNA or RNA. Radioactive end-labeling.

Southern Blotting
Ed Southern, University of Edinburgh, Swiss Science Foundation, 1975 — Detection of specific DNA sequences using fragments separated by gel electrophoresis

Cloning Vectors
Paul Berg, Stanford University, NIGMS, 1972 — First successful generation of recombinant DNA molecules
Stanley Cohen, University of Conn[illegible], NIGMS/NIAID, 1973 — First use of plasmid vectors for gene cloning (pSC101)
Stanley Falkow, Stanford University, NSF/NCI/HHMI, 1977 — Development of a multipurpose cloning system (pBR322)

RNA Polymerase
Michael Chamberlin, Univ. of California, Berkeley, NIGMS, 1970-1982 — Development of T7 and SP6 RNA polymerase promoters

Restriction Enzymes
Hamilton Smith, Johns Hopkins University, NIAID, 1970 — Discovery of the first sequence-specific endonuclease
Daniel Nathans, Johns Hopkins University, NIGMS, 1970 — Demonstration that DNA fragments are discrete on a gel

Reverse Transcriptase
David Baltimore, Massachusetts Institute of Technology, NIAID/ACS, 1970 — Discovery of RNA-dependent DNA polymerase activity
Howard Temin, University of Wisconsin, NCI, 1970 — (simultaneous observation)

PCR Automation
Oliver Smithies, University of Wisconsin, NIGMS/NHLBI, 19[illegible] — Automatic temperature shift apparatus for polymerase chain reaction

Taq Polymerase
David Gelfand/Kary Mullis, Cetus Corporation, 1988 — PCR amplification with thermostable Taq polymerase

PCR Polymerase Chain Reaction
Kary Mullis, Cetus Corporation, 1985 — Oligonucleotide-mediated enzymatic amplification of specific sequences in genomic DNA
Norman Arnheim, University of Southern California, NIGMS, 1985 — First medical test using PCR – diagnostic test for sickle cell anemia

Klenow pol I
Hans Klenow, Carlsberg, Germany, 1970-1974 — Proteolytic fragment of DNA polymerase I lacking the 5'-3' exonuclease activity
Arthur Kornberg, Stanford University, NIGMS/NSF, 1969 — (simultaneous observation)

DNA pol I
Arthur Kornberg, Stanford University, NIGMS/NSF, 1958-1969 — Purification and characterization of DNA polymerase I from E. coli

DNA/DNA Hybridization
Roy Britten/Eric Davidson, California Institute of Tech., NICHD/NSF/ACS, 1971 — Measurement of DNA sequence complexity by reassociation in solution (COT curves)

Oligonucleotide Primers
Ray Wu, Cornell University, NIGMS, 1972 — Use of oligonucleotides for DNA sequence analysis

T. aquaticus
Hudson Freeze, Indiana University, NSF/AEC/NASA, 1969 — Isolation and characterization of thermophilic bacteria *Thermus aquaticus*

Chemical Synthesis of DNA
Marvin Caruthers, University of Colorado, NIGMS, 1981 — Solid-phase phosphoramidite modification of phosphite method
Robert Letsinger, Northwestern University, NIGMS, 1965-1976 — Synthesis of oligonucleotides by phosphite triester intermediates
H. Gobind Khorana, Massachusetts Institute of Technology, NCI, 1958 — General method for the chemical synthesis of deoxyribo-dinucleotides

DNA Sequencing
Walter Gilbert, Harvard University, NIGMS, 1977 — Method for sequencing DNA by chemical modification
Fred Sanger, MRC, Great Britain, 1977 — DNA sequencing with chain-terminating inhibitors

Abbreviations

ACS	American Cancer Society
‸EC	Atomic Energy Commission
HHMI	Howard Hughes Medical Institute
MRC	Medical Research Council
NASA	National Aeronautics and Space Administration
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIGMS	National Institute of General Medical Sciences
NSF	National Science Foundation

Legend

▆ ⊘ = NIGMS support of a specific research advance

☐ = Research not supported by NIGMS

January 1994

CURRICULUM VITAE
MARVIN CASSMAN, PH.D.

POSITION:	Acting Director, National Institute of General Medical Sciences (NIGMS), National Institutes of Health (NIH)
BIRTHPLACE and DATE:	Chicago, Illinois April 4, 1936
EDUCATION:	B.A., University of Chicago, 1954 B.S., University of Chicago, 1957 M.S., University of Chicago, 1959 Ph.D., Albert Einstein Medical School, 1965
EXPERIENCE:	Acting Director, NIGMS, NIH, 1993-present Deputy Director, NIGMS, NIH, 1989-present Director, Biophysics and Physiological Sciences Program, NIGMS, NIH, 1985-1989 Senior Policy Analyst, Office of Science and Technology Policy, 1985-1986 Staff, House Subcommittee in Science and Technology Policy, 1982-1983 Chief, Molecular Basis of Disease Section, Cellular and Molecular Basis of Disease Program, NIGMS, NIH, 1978-1984 Health Scientist Administrator, Cellular and Molecular Basis of Disease Program, NIGMS, NIH, 1975-1978 Assistant Professor, University of California, Santa Barbara, 1967-1974 NIH Postdoctoral Fellow, University of California, Berkeley, 1965-1967 Research Fellow, Northwestern University Medical School, 1959-1961
ASSOCIATION MEMBERSHIPS:	International AIDS Society American Association for the Advancement of Science Biophysical Society
SPECIAL AWARDS or CITATIONS:	Presidential Meritorious Executive Rank Award, 1991 Senior Executive Service Awards; 1987, 1988, 1989, 1990 NIH Director's Award, 1983 NIH Quality Increase Award, 1980
COMMITTEE MEMBERSHIPS:	NSTC Committee on Fundamental Science, 1994 PHS Human Radiation Studies Working Group, 1994 NIH Tuberculosis Executive Committee, 1993-present NIH Task Force on the Commercialization of Intellectual Property Rights from NIH Funded Extramural Research, 1993-present NIH Bioengineering Working Group, 1993-present NIH Intramural Research Infrastructure Subcommittee, 1993-present Chemical and Engineering News Advisory Board, 1993-present NSF Advisory Committee for Biological Sciences, 1993-present Chemical and Engineering News Advisory Board, 1993-present NSF Advisory Committee for Biological Sciences, 1993-present Shannon Awards Committee, 1991-1993 NIH AIDS Executive Committee, 1987-1993

POTENTIAL IMPACT OF BUDGET REDUCTIONS

Mr. PORTER. Dr. Cassman, I'm going to give you a chance to catch your breath and direct my first question to Dr. Varmus, if he's prepared to answer. I'm not sure necessarily that he may be, but I want to ask it anyway. You've talked about controlling, preventing infections and disease, you've talked about industrial spinoffs from discoveries made and the applications that lead to a growing economy, more jobs, more trade.

Dr. Varmus, last week the House Budget Committee released a list of illustrative cuts that would achieve savings required to finance a reduction in the deficit, and as you know, the list included a five-year savings of $2,462,000,000 from NIH, roughly $500,000,000 per year. I wonder if you could give us your reaction to that illustrative cut of the Budget Committee, and what such a cut would mean to biomedical research at NIH if in fact it were enacted?

Dr. VARMUS. Well, I won't mince words. That half million cut from the 1995 appropriation would be roughly $1,000,000,000, nearly a billion dollars below what the President has recommended for fiscal year 1996 for NIH. That would reduce our anticipated success rate from around 24 percent to about 15 percent. That would be a devastating blow to biomedical research. It would send the wrong signal to those who are entering the field that Dr. Cassman just described to you in such glowing terms and it would have repercussions that would affect every aspect of American life for decades.

MOLECULAR RESEARCH

Mr. PORTER. Dr. Cassman, your Institute supports basic research almost exclusively. What trends do you observe in the basic research grant applications that you've received over the last five years? Is it fair to say that molecular level research now dominates your basic research portfolio? And additionally, we hear on occasion concerns raised that NIH is placing too much emphasis on molecular research, rather than research involving the whole cell or the whole animal. How do you respond to that concern?

Dr. CASSMAN. Mr. Porter, I would say that actually for the last 40 years, probably, the emphasis has been increasingly on molecular level research, and for good reasons. The studies of the molecular basis of disease and the studies of the molecular basis of biological phenomena have provided incredible insights into how the cell works.

I would also say, however, that I think that although at the moment, you are quite correct, we are largely supporting research at the molecular level, although that includes cellular research as well, using the techniques of molecular biology. I have a sense that we are beginning to reintegrate a great deal of what we have learned already. With fundamental knowledge of molecular action and biological systems, we are beginning to understand how larger, more integrated systems work.

I think this is clear from a number of directions, and it's a growing effort. But you're unquestionably right; currently the major effort is at a molecular level, because we still have a great deal to learn about what goes on at this fundamental level of biological systems.

RESEARCH TRAINING

Mr. PORTER. Your Institute supports a large share of research training at NIH. Last week we discussed with Dr. Varmus the increase over the last 10 years in the number of researchers trained and applying for NIH grants. Dr. Varmus pointed out that NIH supports only 15 to 20 percent of the research training positions, and so has only limited control over the supply issue.

But doesn't NIH find itself in the position that because of outside forces producing more scientists, it is confronted with declining success rates, even though it is funding the same total number of grants?

Dr. CASSMAN. I think that's probably correct, Mr. Porter. There has been a great deal of discussion of this in academia and within NIH. Our Council is discussing this very question. I believe what we provide to the students through our training programs, and the universities provide, is an opportunity—opportunity to go into, I would say, the most exciting field of research that currently exists. As the students begin to see that these opportunities do not match their expectations, they will go elsewhere.

This has already happened in other areas of science. I don't believe that the NIH can or should control how the universities conduct their business, and we certainly shouldn't control how students make decisions about their careers and their lives. We can encourage the best students, who will still have as many opportunities as they had in the past. We can still encourage the best students to enter this field, and I think they will have a rewarding career.

Mr. PORTER. Then you don't think NIH should communicate to the graduate schools that they perhaps should tailor their doctoral programs to the likely volume of NIH grants, particularly in this budgetary environment we find ourselves in?

Dr. CASSMAN. We haven't had a great deal of success in encouraging universities to do anything that they didn't want to do. And I'm not sure that we're going to be terribly successful in this either. Actually they're quite knowledgeable about how well we're doing and consequently how well they're doing. But I don't believe we can or should instruct them in how they should conduct their business.

Mr. PORTER. What kind of data exists to evaluate NIH research training programs? How does the eventual funding success of researchers supported by NIH training grants compare to those who do not receive NIH funding?

Dr. CASSMAN. Since the 1960s, there has been at least one major study of NIH training programs each decade. And there is one currently underway. Each one of these studies has shown the same thing, that NIH-supported trainees do better than any comparison group against which they're measured. They do better than students at the same institutions that are not supported with NIH training, and they do significantly better than students at institutions that have no NIH training grants. And this is by virtually any measure that's been used.

Mr. PORTER. How do you deal with the problem of skimming? Are those who receive NIH support the best and the brightest who would have done well regardless of NIH support?

Dr. CASSMAN. That's a very good question, Mr. Porter. There's no direct way to answer that, except to say that what we have done through the training grants is provide an environment in which the best students can flourish. We encourage multidisciplinary research.

At one time in fact, we essentially had perhaps the only accomplishment in getting universities to do things slightly differently. We pushed multidisciplinary research training at a time when departmentally-based research training was still the primary way of operating. Now, virtually every institution operates in a multidisciplinary training mode. I think it's in fact been one of the great achievements of the training programs. And I think it's an example of how we provide a milieu in which the best students can flourish.

SUCCESS RATE

Mr. PORTER. Your success rate in 1995 is expected to be quite high, 40 percent, because of the change in the length of grants which causes two years worth of grants to come up for re-competition in a single year. Your success rate in 1996 is also projected to be higher than most other institutes at about 35 percent. What accounts for this?

Dr. CASSMAN. Yes, I'm glad you asked that question. As you quite correctly pointed out, this year's very high numbers are an anomaly. The numbers of last year and next year are in fact the norm for NIGMS. If you look back over the last 10 years, there's only one year in which the General Medical Sciences Institute has not had a success rate that was significantly higher than the NIH norm.

The reason for this is actually quite simple. We put all our money into one pot. Roughly eighty percent of our budget goes into investigator-initiated research grants. We put virtually nothing into contracts, and very little into centers. We have a total of nine centers. In fact, we don't even support very many program projects for multiple investigators. Even though they are investigator-initiated, these are multiple investigator grants.

The bulk of our resources go into single investigator, investigator-initiated research grants. Perhaps it's not surprising, because we put so much emphasis on it, that we should do comparatively better than the other Institutes that have a more diverse set of approaches to reach their mission.

MINORITY PROGRAMS

Mr. PORTER. How are you planning to use the $3,375,000 that was transferred to your Institute from the 1995 Office of the Director appropriation?

Dr. CASSMAN. Those funds are being used in our minority programs. Some of them will be used for our MARC, Minority Access to Research Careers training program, and others to the MBRS, the Minority Biomedical Research Support program, which supports research as opposed to training.

Mr. PORTER. We understand you've been conducting a review of those training programs, particularly the MARC program. What have you concluded from the review, and what plans do you have to revise the programs, if any?

Dr. CASSMAN. The study is not quite complete. We hope to have all the data available and hopefully analyzed within the next one or two months. And so I'm a little uncomfortable about addressing that just yet.

But even apart from that, the new director of our MORE program, Minority Opportunities in Research program, Dr. Clifton Poodry, has been undertaking a careful examination of all our minority programs, in connection with a variety of advisors, including extensive discussion with our Advisory Council. Using all the information available to us, we will try to optimize our resources for these very important programs.

Mr. PORTER. Do you have any plans to expand your activities encouraging minority students to enter science in high school or even earlier? Isn't an important segment of the minority pool already lost by the time they enter college if you don't reach them earlier?

Dr. CASSMAN. You're absolutely right, Mr. Porter. That's an important problem. It's not clear to me that that is a problem that we have either the resources or perhaps even the ability to address, except on a local level. And Dr. Varmus, I believe, has talked already about this and some of the efforts NIH is making. I think, unless something changes drastically, we have to focus the resources we have in the areas that we feel competent in addressing, which is primarily at graduate and higher levels and somewhat in undergraduate education.

Mr. PORTER. Can you do any outreach with other organizations that could deal with this problem and influence them?

Dr. CASSMAN. Absolutely. We have. We coordinate, in fact, with a variety of branches of the Government, with NSF and with the Department of Education. Several members of our staff serve on joint committees looking at this. And we are also talking to a number of the professional societies about addressing this problem as well. The National Academy of Sciences, as Dr. Varmus just reminded me, is extremely interested in this issue.

Mr. PORTER. Let's talk about retention of minority students when they enter doctor of life sciences programs. What are dropout rates, and how do they compare with the average for these kinds of disciplines?

Dr. CASSMAN. That's something that we're currently examining through the study that's been ongoing with the MARC program. I would rather at this point not give you a firm answer, but I'll be happy to transmit that data as soon as we have it available.

REVIEW OF DIVISION OF RESEARCH GRANTS

Mr. PORTER. Dr. Cassman, I'd like to ask you a question in your capacity as head of the group that is reviewing the structure of the Division of Research Grants. We understand your panel is on a fairly fast track to produce its recommendations. What are the fundamental questions about the grant review process and its management that you feel need to be answered?

Dr. CASSMAN. Yes, we hope to get a report to Dr. Varmus within the next month. The questions we are asking are not so much about the details of peer review, which have been intensively examined. We're looking rather at the structure of the Division of Research Grants, how it operates within the NIH, and coordinates with the various groups to which it provides essential services. We plan to use information, in part drawn from the outside community, to modify and improve its activities. The review involves a variety of issues that are related primarily to structure rather than to details of the functioning of the system, such as the operation of the peer review panels?

STATE OF BIOTECHNOLOGY INDUSTRY

Mr. PORTER. Your Institute supports research which has been very important in the development of the biotechnology industry. What's your assessment of the state of the industry today? Press reports variously describe it as an industry of tremendous potential and growth, or as beleaguered with its access to capital markets threatened.

Dr. CASSMAN. I suspect both of those things are true. The biotechnology industry is in a period of extraordinary development. New ideas, new concepts and products are continuously coming forward. It's a highly competitive environment. And I suspect that some companies will fail. But in the process, we will generate a very healthy and active new industry, provided that the fundamental research that they need to continue is available and of course, the capital as well.

BIOTECHNOLOGY TRAINING

Mr. PORTER. You support a biotechnology training program which you have not been able to fund at originally anticipated levels. As one of the principal beneficiaries of this training, have biotechnology companies made any effort to contribute to the cost of the program?

Dr. CASSMAN. The biotech companies contribute in one specific way. There is a required rotation by students in the biotech training programs, that is, they are required to spend time in industry, either in summer or as part of their thesis development. Beyond that, they have not contributed directly to the support of students. I'm not sure that's entirely because they don't want to. There are some difficulties in mingling funds.

TRAUMA AND BURN RESEARCH

Mr. PORTER. You've traditionally had a program in burn research. Out of curiosity, why is that effort located in your Institute rather than the National Institute of Arthritis and Musculoskeletal and Skin Diseases?

Dr. CASSMAN. The General Medical Sciences Institute has had the responsibility for programs that cross a multitude of different Institutes. The trauma and burn program has a variety of components that are related to many Institutes at NIH. Neuroscience for one would be of interest to the Neurology Institute. There's a whole variety of Institutes that could be involved in some aspect of trauma and burn research. But since this is a unified area that was considered of importance, we have been responsible for dealing with it, rather than assigning it to any specific other Institute.

SIGNIFICANCE TO INDUSTRY OF NIH RESEARCH

Mr. PORTER. Mr. Wicker is here now, so we're going to give him a chance to ask questions if he wishes to. But let me end by asking you a spinoff question from the one I asked Dr. Varmus. If NIH didn't exist, what kind of biotechnology industry would we have today? And if NIH were level funded, or alternatively, would receive the kinds of cuts suggested by the Budget Committee, what would that mean to the biotechnology industry?

Dr. CASSMAN. I think the answer to the first question is fairly clear. If NIH didn't exist, I doubt if at this point in time there would be a biotechnology industry. I'm not quite sure——

Mr. PORTER. The United States wouldn't have one?

Dr. CASSMAN. If it had one, it would be fairly rudimentary. Because we would be way behind the curve, relative to other countries.

As for what it will mean for the future, my response is very similar to that of Dr. Varmus. We will reduce the output of the fundamental knowledge that the biotechnology industry uses to generate its product.

A number of people have mentioned that industry has increased its contribution to national research efforts. But in fact, that contribution between roughly 1987 and 1993 has only been from 3 to 7 percent to support the total academic research and development. And as far as basic research is concerned, it is primarily the Federal Government that does it. And within the Federal Government, the National Institutes of Health have made the primary contribution. If we don't make it, it isn't going to be made up elsewhere.

Mr. PORTER. Is it a fair statement to say there's a direct correlation between the investment in biomedical research and the growth in success of the biotechnology industry?

Dr. CASSMAN. Oh, absolutely. I think that is perfectly clear.

Dr. VARMUS. There's a very good illustration of the relationship between investment in NIH-supported research and the investment in research made by biotech and pharmaceutical houses reported in an article that appeared in the *Wall Street Journal* last week. This article discussed the new wave of excitement in developing pharmaceutical approaches toward an activation of genes called RAS genes, proteins made by those genes in the treatment of cancer.

And it becomes very apparent as one reads that article that this kind of frenzied entrepreneurial activity, with all of its investment in exciting research that portends major changes in clinical approaches to cancer, could not have happened without the initial observations about cancer genes, and equally importantly, without new developments that have occurred in the academic sector over the last 20 years supported by NIH.

Mr. PORTER. If I had assembled the CEOs of the major pharmaceutical companies at the table here, and I asked them whether we should put NIH at a high priority in our funding, and then I asked them the other questions that I've just asked you, what do you think their answers would be?

Dr. VARMUS. Very similar to my own.

Mr. PORTER. They would say, this is high priority, keep up the funding, or we will be hurt?

Dr. VARMUS. I believe so.

Dr. CASSMAN. Mr. Porter, someone not at this table, obviously, actually asked that question. A number of years ago Ernst & Young did a study of the biotechnology industry. And they asked the CEOs if the Federal Government were to budget funds to support biotechnology, how would the industry allocate the money. Additional research was overwhelmingly identified as the number one need. I will quote what the report says. It says, "This finding is a ringing affirmation of the criticality of Government-sponsored research, which stems primarily from the NIH." And I think that says about all that needs to be said about it.

Mr. PORTER. Mr. Wicker?

AGENCY INTERACTIONS REGARDING CANCER RESEARCH

Mr. WICKER. Thank you, Mr. Chairman, and I'll simply direct this question to whoever would like to answer it. It deals with cell research, in terms of dealing with cancer. I'd like for one of you to comment about how the various agencies interact in the fight against cancer.

Dr. VARMUS. As you know, Mr. Wicker, the National Cancer Institute has a budget that goes to about $2,100,000,000. And it is the component of the NIH where not only is most of the cancer research done, but also it has the responsibility for carrying out the presidential war on cancer.

Nevertheless, there is a tremendous amount of research in other Institutes that addresses cancer directly because, for example, the cancer in question is in the purview of that Institute. As an example, in the National Institute of Neurological Disorders and Stroke, there is an enormous interest in brain tumors. In the Eye Institute, there's an interest in tumors of the eye.

But in addition, many of the Institutes find themselves involved in the study of cancer, because their fundamental research impinges on problems of cancer. A very simple example is a place you visited with us not too long ago, the National Center for Human Genome Research, where the investigation of genes that are known to be implicated in the causation of cancer are being studied as a part of the Human Genome Project. In that context, studies of the breast cancer gene and colon cancer genes and many others, become a natural activity.

Virtually every Institute has some role in cancer research. But the major source of funding and the major source of activity and the leader when there is inter-agency activity would be the National Cancer Institute.

Mr. WICKER. My question was further about how the agencies interact with each other?

Dr. VARMUS. How the Institutes would interact?

Mr. WICKER. Right.

Dr. VARMUS. Most of the interactions, many of them are informal, through discussions that are carried out by scientists. Some of them are more formal, for example, there are co-funding agreements. There are projects that are carried out through collaborative research.

Very frequently, investigators at academic institutions will be funded by different Institutes and will be interacting in that way. There are a number of avenues by which such things occur. Frequently meetings are sponsored by multiple Institutes. I just went myself quite recently to a workshop on glioblastoma that was funded by the Cancer Institute and the Neurology Institute and other agencies.

There are in addition interactions between NIH and other Public Health Service agencies, in particular the CDC, that concern matters of cancer research.

RESEARCH ON THE PROSTATE

Mr. WICKER. Could one of you comment about Dr. David Russell's work in the University of Texas in studying the male hormone DHT and its relationship to prostate enlargement?

Dr. CASSMAN. Yes. Dr. Russell is one of our grantees, and has been looking at the biosynthesis of the male hormone androgen for some years. In the process, he's been able to identify two different forms of an enzyme that's involved in the synthesis of this hormone. It turns out that one of these is related to, I don't believe it's actually to prostate cancer, but it's related to prostate enlargement. And the other one has to do primarily with male pattern baldness, which is interesting, but too late for me, I'm afraid.

POTENTIAL IMPACT OF BUDGET REDUCTIONS

Mr. WICKER. All right. Mr. Chairman, let me apologize, if this question is redundant as I had another subcommittee meeting at the same time. With regard to NIGMS, have you had a chance to look at Mr. Kasich's recommendations last week, and can you tell me how you think implementation of that proposal would affect NIGMS?

Dr. CASSMAN. The reduction of 5 percent, I believe it was? Yes, we would do a good bit less, and what we would do we would do more slowly. We would have to reduce both numbers and dollars for our grantees. And I think it would cause considerable difficulties. The promise of a lot of lines of research, which are currently still active, would be substantially reduced.

Dr. VARMUS. It is perhaps important to add to the answer I gave before, which was a question from Mr. Porter about the effect of the proposed reduction on NIH. I answered in the context of 1996. It's also important to point out that as that level is maintained without change over the succeeding several years, the disparity between the buying power of those dollars and what we would expect to do with the tools of biological research available, would only widen. And by the year 2000, the difference between what we are spending now on biomedical research and what we would be spending then would be as much as 29 percent. That would have a tremendous effect on our ability to pursue the Nation's health.

Mr. WICKER. Thank you, Mr. Chairman.

Mr. PORTER. I have no further questions for you, and it's exactly 11:00. So we thank you very much, Dr. Cassman.

Dr. CASSMAN. Thank you, Mr. Porter.

Mr. PORTER. We appreciate very much your good testimony this morning. You did an excellent job.

[The following questions were submitted to be answered for the record:]

MINORITY OPPORTUNITIES IN RESEARCH FUNDING

Mr. Porter: Identify the co-funding of the MARC and MBRS programs from other Institutes in 1995 and 1996.

Dr. Cassman: The projected co-funding of the Minority Access to Research Careers (MARC) and Minority Biomedical Research Support (MBRS) programs from other Institutes in 1995 and 1996 is listed by Institute below.

MARC Program Co-funding
(dollars in thousands)

Institute	FY 1995 Amount	FY 1996 Amount
NCI	$128	$128
NHLBI	57	57
NIDR	43	43
NIDDK	144	144
NINDS	16	16
NIAID	39	39
NICHD	44	44
NEI	0	0
NIEHS	128	128
NIA	49	49
NIAMS	32	32
NIDCD	10	10
NCRR	0	0
NCNR	2	2
NCHGR	0	0
NLM	0	0
NIMH	0	0
NIDA	0	0
NIAAA	5	5
TOTAL	$697	$697

MBRS Program Co-funding
(dollars in thousands)

Institute	FY 1995 Amount	FY 1996 Amount
NCI	$3,099	$3,316
NHLBI	2,753	2,803
NIDR	196	202
NIDDK	1,794	1,794
NINDS	313	320
NIAID	713	738
NICHD	585	602
NEI	364	375
NIEHS	462	462
NIA	907	933
NIAMS	452	465
NIDCD	575	586
NCRR	0	0
NCNR	0	0
NCHGR	0	0
NLM	0	0
NIMH	0	0
NIDA	0	0
NIAAA	312	321
Total, Non-AIDS	12,525	12,917
NIAID (AIDS)	428	457
TOTAL	$12,953	$13,374

Mr. Porter: Provide a mechanism table for the MARC program 1994-1996.

Dr. Cassman: Below is a mechanism table for the MARC Program FY 1994-FY 1996.

MARC Program
FY 1994 - FY 1996
Mechanism Table
(dollars in thousands)

	FY 1994 Actual			FY 1995 Estimate			FY 1996 Estimate		
	FTTP	No.	Amt.	FTTP	No.	Amt.	FTTP	No.	Amt.
Research Grants		0	$0		0	$0		0	$0
Centers		0	$0		0	$0		0	$0
Other Research:									
Conference/ Co-op Agree.		1	142		0	0		0	0
Training:									
Individual:									
Predoctorals	78	78	1,903	96	96	2,345	96	96	2,423
Postdoctorals	1	1	35	5	5	147	5	5	151
Subtotal:	79	79	1,938	101	101	2,492	101	101	2,574
Institutional:									
Predoctorals	566	66	12,706	668	75	14,161	668	75	15,661
Postdoctorals	0	0	0	0	0	0	0	0	0
Subtotal:	566	66	12,706	668	75	14,161	668	75	15,661
Total: Training	645	145	14,644	769	176	16,653	769	176	18,235
TOTAL: MARC	645	146	$14,786	769	176	$16,653	769	176	$18,235

NRSA Training Stipend Levels

Mr. Porter: What is the range of pre- and post-doctoral training stipends in 1995?

Dr. Cassman: Predoctoral stipends for traditional training programs are set at $10,008 per trainee for fiscal year 1995.

Postdoctoral stipends range from $19,608 for a fellow with less than one year of experience to $32,300 for a fellow with seven or more years of experience.

LIFE SCIENCES Ph.D'S GRANTED 1989-1993

Mr. Porter: Provide data on the number of life sciences Ph.D.s granted to U.S. citizens over the last five years. What percent of these are from underrepresented minority groups?

Dr. Cassman: According to the National Research Council Summary Reports for 1989-1993, Doctorate Recipients from United States Universities, the number of life sciences Ph.D.s granted to U.S. citizens over the last five years, and the percent of these conferred to underrepresented minority groups is as follows.

Life Sciences Ph.D.s	1989	1990	1991	1992	1993
U.S. Citizens of Known Race and Ethnicities	4,450	4,542	4,647	4,640	4,782
Underrepresented Minorities					
Number	170	186	206	220	262
Percent of Total Citizens	3.8%	4.1%	4.4%	4.7%	5.5%
All Others					
Number	4,280	4356	4,441	4,420	4,520
Percent of Total Citizens	96.2%	95.9%	95.6%	95.3%	94.5%

UNDERREPRESENTED MINORITY ENROLLMENT

Mr. Porter: What share of minority students attend minority versus majority schools?

Dr. Cassman: The most recent data available on the enrollments of minority students at undergraduate and graduate institutions is for academic year 1991. At that time, 72.8 percent of the underrepresented minority U.S. resident students enrolled at the undergraduate level attended majority schools; while 27.2 percent attended minority schools. At the graduate level, 90.8 percent of the enrolled underrepresented minority U.S. resident students were enrolled at majority schools; while 9.2 percent attended minority schools. This information was obtained from the Integrated Postsecondary Education Data System (IPEDS), a data system comprised of surveys of universities and colleges conducted by the U.S. Department of Education National Center for Education Statistics.

Mr.Porter: What share of MARC graduates go on to complete a doctoral degree, and how many go on to receive NIH grant awards?

Dr. Cassman: Our best estimates are that about 12.5 (+/- 2.5) percent of former MARC trainees go on to complete the Ph.D. or an M.D./Ph.D., and that about 25.3 (+/- 2.2) percent receive M.D. degrees. A total of 491 former trainees have received M.D. degrees so far. A total of 166 former MARC trainees have reported receiving a Ph.D. or M.D./Ph.D. Of the Ph.D. recipients, few have received NIH grants: one has received a research project grant, one has received a First Independent Research Support and Transition Award, one has received a Minority School Faculty Development Award, and two have received Minority Biomedical Research Support grants. In addition, 10 have received postdoctoral fellowships. [Note that these figures do not include those who may have received grants from other Federal agencies, or those who may be subproject PIs on NIH program project grants or centers.]

Mr. Porter: What is the representation of Hispanics and African Americans among life science Ph.D.s awarded in the last five years versus their proportion of the general population?

Dr. Cassman: The table below displays the representation of Hispanics and African Americans among life science Ph.D.s awarded in the last five years versus their proportion of the general population.

	1989	1990	1991	1992	1993
Blacks					
Percent of Total Ph.D.s	2.1%	1.9%	2.3%	2.3%	2.9%
Percent of Total Pop. in 1990 Census	12.1%	12.1%	12.1%	12.1%	12.1%
Hispanics					
Percent of Total Ph.D.s	2.2%	2.7%	2.5%	2.7%	3.0%
Percent of Total Pop. in 1990 Census	8.99%	8.99%	8.99%	8.99%	8.99%

This information was obtained from the National Research Council Summary Reports for 1989-1993, Doctorate Recipients from United States Universities and the 1990 Report from the Bureau of the Census.

NIGMS BASIC RESEARCH GOALS

Mr. Dickey: What are the basic goals of the research conducted at NIGMS?

Dr. Cassman: NIGMS-supported research is aimed at increasing understanding of fundamental life processes. Such understanding is necessary to provide the knowledge and theories that enable scientists to make advances in the treatment, cure, or prevention of disease. NIGMS-supported studies also yield new research tools and technologies that are used in the disease-targeted studies of other NIH components and the biotechnology industry.

Mr. Dickey: How do you assure that research done at NIGMS is not duplicated at other institutes at NIH?

Dr. Cassman: Every two years the Division of Research Grants (DRG) publishes a manual titled, "Referral Guidelines for Funding Components of PHS". This manual is the result of intensive discussions between the various components of the PHS, including NIGMS. It is designed to clearly state the areas of research interest of each component and to resolve any potential overlap of research interests. All research project applications are sent to the DRG and the DRG uses this manual to determine which institute will be assigned an application. In this way the possibility of duplication of research by another institute is greatly reduced.

RESEARCH ACCOMPLISHMENTS

Mr. Dickey: What recent progress has been made at NIGMS in the area of hypertension?

Dr. Cassman: As noted above, NIGMS grantees often design new tools and laboratory techniques that can be used to increase knowledge about the mechanisms involved in specific diseases. Frequently, these tools are the result of studies to answer basic research questions. For example, NIGMS supported the development of a technique to create mice with specific genes that are "knocked out." Researchers can use these mice to determine how the missing genes function in development or in specific diseases. Because humans and mice share so many of the same genes, these studies have important implications for understanding human disease.

One of the scientists who developed the technique has now used it to create a mouse model for hypertension. With support from NIGMS and the National Heart, Lung, and Blood Institute, he has demonstrated a direct, causal relationship between the maintenance of blood pressure in these mice and the expression of two molecules, called angiotensinogen (AGT) and atrial natriuretic peptide (ANP). Mice with more copies of the AGT gene have higher blood pressure, and mice with reduced expression of the ANP gene are vulnerable to salt-sensitive hypertension. The availability of this mouse model is expected to make it easier for scientists to study hypertension, which should enable them to develop better ways to combat it in humans.

Mr. Dickey: How has the development of the Jellyfish Protein aided your research?

Dr. Cassman: The green fluorescent protein (GFP) from a jelly fish has become an important tool for a variety of biological studies. For example, when the gene for GFP is linked to a specific location in the genetic material of a worm, the green fluorescence appears every time that part of the gene is activated. This is a way to follow the developmental process in the worm, since the same worm can be followed over time. In the past, fluorescent or other labels could only be used by sacrificing the worm or other organism at different points in development, a time-consuming process that had many difficulties attached to it.

Many other uses are envisaged: a marker for in situ studies of cell growth and migration; a tool for selectively killing transformed cells if a laser light can be found that is absorbed only by GFP-expressing cells; and a visible marker for identifying animals and tissues in which foreign genes have been introduced.

RESEARCH TRAINING PIPELINE

Mr Stokes: What is the state of the biomedical research pipeline in general, and what is the state with respect to women? Minorities? African Americans?

Dr. Cassman: In many fields, both women and minorities face problems of underrepresentation. However, in the biomedical sciences it is minorities and not women who remain significantly underrepresented. Over the 10-year period from 1983 to 1993, the proportion of Ph.D.s in the life sciences earned by women has increased from 31 percent to 42 percent. The representation of women in research training programs and among research grant recipients also has been steadily increasing over the past decade. Currently, there is no indication of a critical need to enhance recruitment efforts directed toward women, who represent more than 40 percent of NIH pre- and postdoctoral trainees and fellows in the biomedical sciences, and more than 60 percent of those receiving pre- and postdoctoral support in the behavioral sciences.

A more serious problem for the field has been the underrepresentation of minorities. In 1989, African Americans, Hispanics, and Native Americans made up only about 3 percent of employed doctorates in the biological sciences, while representing roughly 18 percent of the total U.S. workforce. Over the past decade, there has been a slight increase in the number of minorities receiving doctoral degrees in the life sciences. In 1983, only 2.8 percent of U.S. citizens receiving Ph.D.s in these fields were underrepresented minorities; in 1993, minorities represented 5.5 percent of the Ph.D. recipients. African Americans represented 1.5 percent of the life science Ph.D.s received by U.S. citizens in 1983 and 2.6 percent in 1993. The goal of existing NIGMS programs is to ensure further and more rapid progress in this area, and new ways are sought continually to meet this critical need.

One component of the NIGMS, the Division of Minority Opportunities in Research (MORE), serves as the focal point for NIGMS efforts to increase the number and capabilities of minority individuals engaged in biomedical research. The MORE Division, through its various components, provides special training opportunities in the biomedical sciences for students and faculty at institutions with substantial minority enrollments as well as conference support to organizations and institutions that are active in the recruitment and retention of minority scientists. Institutional research capabilities are strengthened through the provision of faculty and student participation in research at 2- and 4-year colleges, universities, and health professional schools with substantial minority enrollments. The development of new and innovative programs and the expansion of existing programs is encouraged to improve the academic competitiveness of underrepresented minority students, facilitating their transition into the next stage towards careers in biomedical research.

NRSA, MARC AND MBRS FUNDING

Mr. Stokes: How much is included in the FY 1996 budget request for each of the following programs -- the National Research Training Service Awards Program, the MARC Program, and the MBRS Program? How does the FY 1996 budget request level compare with the FY 1995 and FY 1994 funding level for each?

Dr. Cassman: The following table reflects NIGMS' support for National Research Service Awards, MARC and the National Predoctoral Program:

NRSA Training
(dollars in thousands)

	FY 1994	FY 1995	FY 1996
MARC	$14,644	$16,653	$18,235
National Predoctoral	2,879	2,876	2,960
Other Traditional Training	85,229	84,875	86,237
Total, NRSA	$102,752	$104,404	$107,432

NIH and NIGMS Support for the MBRS Program are as follows:

MBRS Program
(dollars in thousands)

	FY 1994	FY 1995	FY 1996
NIGMS	$34,795	$37,105	$38,181
NIH	13,247	12,953	13,374
TOTAL	$48,042	$50,058	$51,555

Mr. Stokes: Each of these programs reflect what percentage of the Institute's total budget?

Dr. Cassman: The FY 1996 budget request for the National Research Service Awards Program reflects 11.5 percent of the Institute's total budget request. The FY 1996 budget request for the MARC Program reflects 2.0 percent of the Institute's total budget request. The FY 1996 budget request for the MBRS Program reflects 4.1 percent of the Institute's total budget request.

NUMBERS OF TRAINEES

Mr. Stokes: What are the numbers of individual trainees in each of these programs?

Dr. Cassman: The table below displays trainees by category, namely, MARC, National Predoctoral and Other Traditional NRSA Training Programs:

NRSA Trainees

	FY 1994 Trainees	FY 1995 Trainees	FY 1996 Trainees
MARC	645	769	769
National Predoctoral	122	126	126
Other Traditional Training	3,674	3,672	3,672
Total, NRSA Trainees	4,441	4,567	4,567

Beyond this, there were 914 undergraduate and 422 graduate students that participated on MBRS projects as research assistants in FY 1994. It is anticipated that these levels will be maintained in FY 1995 and FY 1996.

BRIDGES PROGRAM

Mr.Stokes: What progress can you report to the Committee on how the Bridges to the Future programs are working?

Dr. Cassman: The BRIDGES Program has been in existence for three years; thus it is still too early to evaluate its effectiveness at achieving long term goals. NIGMS is planning an evaluation to be completed by October 1996. However, some preliminary data is available from eight of the grants initially funded in FY 1992. Eighty-six (86) students have participated in the first year of the program, of these 38 have graduated and transferred into institutions providing the next higher degree program (44%).

There are 52 active BRIDGES grants, of these 17 involve doctoral Bridges, with support for a maximum of 211 student positions for the life of the grants, and 35 baccalaureate Bridges, with support for 944 students. The program involves 80 community and junior colleges, 37 Baccalaureate degree granting institutions, 25 Masters institutions, and 20 Doctoral institutions in 25 states and the Commonwealth of Puerto Rico.

The Program Directors and Coordinators of these grants have met twice, in the spring of 1994 and the spring of 1995, to share their ideas with each other and to learn from their most experienced colleagues what it takes to design a successful Bridges program. The participants in the program have been very excited about the changes taking place in their institutions and the impact of this program on the students.

Mr. Stokes: How much of your Institute's budget is invested in each of these programs and how does it compare with the FY 1995 and FY 1994 funding levels?

Dr. Cassman: Funds for the Bridges Program have been provided by NIH's Office of Research on Minority Health (ORMH). In FY 1994, the funding level was $8,558,000. It is estimated that ORMH will provide $6,000,000 in both FY 1995 and FY 1996 for the Bridges Program.

CELLULAR RESEARCH

Mr. Stokes: As cell-to-cell communication and increasing the understanding of the cellular regulation, appear to be a high priority research area for the Institute. To what extent will increased knowledge in this area of research yield further advances in AIDS, Sickle Cell Disease, Immunodeficiency Diseases, and Breast and Prostate Cancer?

Dr. Cassman: The transmission of signals between cells is a principal mechanism that operates in regulation of cell growth, differentiation and development. Cell interactions are required for immune responses. The specialized cells of the immune system (macrophages, T-cells and B-cells) must exchange signals in order for a normal immune response to occur. In AIDS and immunodeficiency, the immune response is greatly diminished, and therefore a knowledge of cell-cell communication offers an avenue for both understanding the cellular defects in these conditions, and potentially, developing ways of enhancing immune responsiveness.

Growth factors and hormones released by cells signal other normal and cancer cells, telling them how and when to divide, and at what rate. For example, breast and prostate cancers often are responsive to female and male hormones, respectively. Growth factors produced by epithelial cells (EGF) bind to receptors on the surface of breast cancer cells that trigger uncontrolled growth. Furthermore, when cells adhere to surrounding cells, a biochemical sequence is triggered that tells a cell whether to grow in an orderly fashion or pile up in a tumor, whether to remain local or to invade surrounding tissues, and whether to metastasize to distant sites. Therefore, a basic understanding of cell-cell communication, using simple organisms and model systems, provides fundamental knowledge that will contribute to an understanding of the causes and treatment of diseases, such as AIDS, immunodeficiency and cancers of the breast and prostate.

Mr. Stokes: How much is included in the FY 1996 budget request for this area of research, and how does it compare to FY 1995 and FY 1994?

Dr. Cassman: In FY 1994 approximately $5.7 million was provided for research in cell-cell communication. It is estimated that this level will increase by 4 percent each year, for FY 1995 and FY 1996.

FOOD ADDITIVES USED IN ANIMAL FEED

Mr. Stokes: According to your opening statement, recombinant DNA research techniques are affording higher yields of animal feed, and this research is affording American firms the opportunity to make significant inroads into the global market. To what extent are we also assessing the impact of the animal feed additives on human health?

Dr. Cassman: NIGMS supported the basic research that led to the development of recombinant DNA technology, which is now being used for a wide variety of research and industrial purposes, including the production of food additives used in animal feed. Since the study of the impact of these animal feed additives on human health is not basic research, other organizations, such as the Center for Veterinary Medicine of the Food and Drug Administration, would be involved in this assessment. In addition, the National Toxicology Program of the National Institute of Environmental Health Sciences investigates the effects of specific environmental chemicals, and it is possible that certain animal feed additives would be among the chemicals studied.

MINORITY HEALTH

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. While this issue is complex and a multiplicity of factors contribute to the disparity including life style and access to health care, biomedical research does have a key role to play in helping to close the gap. What is your institute's role in the NIH Minority Health Research Initiative?

Dr. Cassman: The role of NIGMS in the NIH Minority Health Initiative has been to encourage underrepresented minorities to prepare for careers in biomedical research through the two Bridges to the Future Programs. One of those programs provides incentives for students attending junior colleges to continue on to pursue Baccalaureate degrees that prepare them for research careers. The other helps students transition from the M.S. degree to the Ph.D. degree in the biomedical sciences.

Mr. Stokes: What is it that you can tell us this year that you could not tell us last year in terms of this area of research and research training?

Dr. Cassman: Over the course of the past year, the number of grants awarded under these two Bridges to the Future Programs has increased. There are now 38 institutions receiving grants for the program bridging the junior college-baccalaureate transition, an increase of 8. There are now 17 institutions receiving grants for the program bridging the Masters degree to Ph.D. degree transition, an increase of 9. The Institute has hosted a second meeting of representatives from all of the grantees of the Bridges to the Future programs in order to promote the exchange of ideas that help programs to succeed. In addition, NIGMS is in the early stages of planning an evaluation of these two programs.

Mr. Stokes: How much is included in your institute's FY 1996 budget request for this area of research and for research training? How does this level of funding compare with that for FY 1995 and FY 1994?

Dr. Cassman: Although the NIGMS administers the Bridges to the Future Program, the funds are provided by the NIH Office of Research on Minority Health. Given this, the NIGMS budget presently includes no funds designated for this program.

CRADAS (COLLABORATIVE RESEARCH AND DEVELOPMENT AGREEMENTS)

Mr. Stokes: A tremendous number of the Institute's research investments have spawned the continuous development of biotechnology companies. To what extent does the Institute use the CRADA mechanism?

Dr. Cassman: NIGMS does not have an intramural laboratory component; therefore, we do not use this mechanism. Rather, our grantees may collaborate with industrial researchers or may, and frequently do, transfer knowledge gained in academic laboratories to commercial enterprises in the biotechnology and other industries.

BIOTECHNOLOGY TRAINING

Mr. Stokes: How much is included in the Institute's FY 1996 budget request for biotechnology and research training? For each of these components, how does the FY 1996 amount compare with the FY 1995 and 1994 level for each?

Dr. Cassman: A comparison of the FY 1996 budget amounts for biotechnology and biotechnology research training supported by NIGMS with those in FY 1995 and FY 1994 is provided in the following table.

Biotechnology Supported by NIGMS
FY 1994 - FY 1996

(Dollars in Thousands)

	FY 1994	FY 1995	FY 1996
Biotechnology Research Projects and related activities.........	$696,885	$722,829	$746,822
Biotechnology Research Training......................	64,810	64,456	65,592
Total Biotechnology Supported by NIGMS.............	$761,695	$787,285	$812,414

MINORITY OPPORTUNITIES IN RESEARCH DIVISION

Mr. Stokes: How many Historically Black Colleges and Universities participate in the Minority Opportunities in Research (MORE) Program?

Dr. Cassman: In Fiscal Year 1994, fifty-seven (57) HBCUs received support from programs supported by the Division of Minority Opportunities in Research.

Mr. Stokes: How does this compare to previous years?

Dr. Cassman: This is a slight increase from fiscal year 1993. In recent years, HBCU participation in the Programs administered by the MORE Division has generally ranged between 50 and 60 institutions.

Mr. Stokes: What is the level of funding provided to HBCUs and how does this compare to previous years?

Dr. Cassman: The table below presents the NIGMS support for HBCUs through the MORE Division's programs for the most recent three fiscal years.

Support for HBCUs by the MORE Division
FY 1992 - FY 1994

(dollars in thousands)

FY 1992	FY 1993	FY 1994
$27,435	$27,543	$31,638

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years, explain.

Dr. Cassman: In 1996, the success rate for NIGMS is projected to be 35 percent. This is right in the middle of the range of success rates for NIGMS over the past five years when those rates ranged from 30 percent to 39 percent. Looking back over ten years, the success rate has ranged from a low of 22 percent in 1990, the year before cost management principles were invoked, to a high of 39 percent, with success rates in the 30's being the norm. The turnover of larger or smaller fractions of the Institute's grant portfolio accounts for most of this variability.

Mr. Stokes: What has been the trend in the average cost of research project grants over the same period?

Dr. Cassman: The average cost of research project grants, in total, has increased approximately 5 percent per year over the 10-year period. Since the implementation of the Cost Management Plan (CMP) in FY 1991, however, the average annual increase has dropped to approximately 4 percent, roughly equal to inflation as measured by the Biomedical Research and Development Price Index (BRDPI).

Mr. Stokes: What is the trend in terms of constant dollars?

Dr. Cassman: In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average annual cost of research project grants, in total, has decreased over the 10 year period by -0.4 percent. Since FY 1991 and the implementation of the Cost Management Plan, the average annual cost change, in constant dollars, has remained approximately the same as in the previous five-year period.

SUCCESS RATES

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Cassman: To comply with Federal mandates, all questions on NIH research grant applications related to race and gender are identified as optional. As a result, NIGMS is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women.

The following table lists success rates of NIGMS research applications received in FY 1994 from those scientists who chose to identify themselves as minorities and from applicants who did not provide their race/ethnicity. Because there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIGMS's support of minority scientists.

Competing Grant Success Rates for Minority Scientists
NIGMS
Fiscal Year 1994

Minorities	37.0%
Unknown	36.1%

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: What is the success rate for research applications received from women researchers?

Dr. Cassman: The following table lists success rates of NIGMS research applications received in FY 1994 from those scientists who chose to identify themselves as women and from applicants who did not provide their gender. Because there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIGMS's support of women scientists.

Competing Grant Success Rates for Women Scientists
NIGMS
Fiscal Year 1994

Women	35.1%
Unknown	50.5%

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: What is the success rate for research applications received from African Americans?

Dr. Cassman: The following table lists success rates of NIGMS research applications received in FY 1994 from those scientists who chose to identify themselves as African American and from applicants whose race/ethnicity was not given. Because there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIGMS's support of African American scientists.

Competing Grant Success Rates for African American Scientists
NIGMS
Fiscal Year 1994

African American	21.4%
Unknown	36.1%

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Cassman: In FY 1994, NIGMS received only four research project grant applications from Historically Black Colleges and Universities. Because of how they fared in peer review, none of those applications were funded.

AVERAGE COSTS OF RESEARCH GRANTS

Mr. Stokes: For the same time period, in real and in constant dollars, what have been the average costs of research project grants awarded to women?

Dr. Cassman: The following table provides the average costs of competing awards, in current and constant (1985) dollars, to scientists who chose to identify themselves as women in selected years over the past decade. As stated previously, questions related to gender are optional on NIH grant applications. As a result, the following data may not provide a true representation of the NIGMS's support of women scientists.

Competing Grant Average Costs for Women Scientists
In Current and Constant Dollars
Fiscal Years 1985, 1989, and 1994
NIGMS
(Dollars in thousands)

	1985		1989		1994	
	Current	Constant	Current	Constant	Current	Constant
Women	$126.4	$126.4	$155.5	$128.3	$198.0	$131.6

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: For the same time period, in real and in constant dollars, what have been the average costs of research project grants awarded to minority researchers?

Dr. Cassman: The following table provides the average costs of competing awards, in current and constant 1985 dollars, to scientists who chose to identify themselves as minorities in selected years over the past decade. (Constant dollars are calculated using the Biomedical Research and Development Price Index.) As stated previously, questions related to race are optional on NIGMS grant applications. As a result, the following table includes a category denoted as "unknown," representing the average costs of competing grant applications awarded to applicants who did not provide their race/ethnicity. In FY 1994, 22 percent of NIGMS applicants chose not to answer the optional questions regarding race/ethnicity, which makes it especially difficult to draw definite conclusions from FY 1994 data. Because there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIGMS's support of minority scientists.

Competing Grant Average Costs for Minority Scientists
In Current and Constant Dollars
Fiscal Years 1985, 1989, and 1994
NIGMS
(Dollars in thousands)

	1985		1989		1994	
	Current	Constant	Current	Constant	Current	Constant
Minorities	$166.2	$166.2	$150.6	$124.3	$204.2	$135.8
Unknown	174.1	174.1	147.9	122.0	181.5	120.7

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: For the same time period, in real and in constant dollars, what have been the average costs of research project grants awarded to African American researchers?

Dr. Cassman: The following table provides the average costs of competing awards, in current and constant 1985 dollars, to scientists who chose to identify themselves as African Americans in selected years over the past decade. The table also includes a category denoted as "unknown," representing the average costs of competing grants awarded to applicants who did not provide their race/ethnicity. Because there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of the NIGMS's support of African American scientists.

Competing Grant Average Costs for African American Scientists
In Current and Constant Dollars
Fiscal Years 1985, 1989, and 1994
NIGMS
(Dollars in thousands)

	1985		1989		1994	
	Current	Constant	Current	Constant	Current	Constant
African Americans	$120.0	$120.0	$118.5	$ 97.8	$187.6	$124.7
Unknown	174.1	174.1	147.9	122.0	181.5	120.7

Source: IMPAC, SAES/DRG/NIH

Mr. Stokes: For the same time period, in real and in constant dollars, what have been the average costs of research project grants awarded to HBCUs?

Dr. Cassman: Costs of awards to Historically Black Colleges and Universities (HBCUs), in current and constant (1985) dollars, for selected years over the past decade are presented below. It should be noted that these costs are based on a single grant for fiscal years 1985 and 1989. There were no research grant awards to HBCUs in 1994.

Competing Grant Average Costs for HBCUs
In Current and Constant Dollars
Fiscal Years 1985, 1989, and 1994
NIGMS
(Dollars in thousands)

	1985		1989		1994	
	Current	Constant	Current	Constant	Current	Constant
HBCUs	$162.4	$162.4	$ 75.3	$ 62.1	$ 0.0	$ 0.0

Source: IMPAC, SAES/DRG/NIH

MINORITY ACCESS TO RESEARCH CAREERS (MARC) FUNDING BY INSTITUTION

Mr. Stokes: Please provide the amount of MARC funding awarded, by institution.

Dr. Cassman: The following table reflects Fiscal Year 1994 MARC funding by institution:

INSTITUTION	INSTITUTIONAL SUPPORT	OTHER RESEARCH	INDIVIDUAL SUPPORT
ALABAMA STATE UNIVERSITY	$257,800		0
ALBANY STATE COLLEGE	154,077		0
AM. SOCIETY FOR MICROBIOLOGY	116,502		0
ARIZONA STATE UNIVERSITY	166,531		0
AUBURN UNIVERSITY AT AUBURN	0		$85,526
BARRY UNIVERSITY	477,582		16,247
BAYLOR COLLEGE OF MEDICINE	0		59,501
BENEDICT COLLEGE	269,323		0
BENNETT COLLEGE	247,111		0
BETHUNE-COOKMAN COLLEGE	134,830		0
BOSTON COLLEGE	0		21,268
CAL. STATE U. LONG BEACH	191,750		0
CAL. STATE U. LOS ANGELES	289,346		0
CAL. STATE U. NORTHRIDGE	207,364		0
CENTRAL ST. U (WILBERFORCE, OH)	133,720		0
CHARLES R. DREW U. OF MED & SCI	176,567		0
CHILDREN'S HOSPITAL (BOSTON)	0		17,894
CITY COLLEGE OF NEW YORK	272,172		0
CLARK ATLANTA UNIVERSITY	562,627		17,912
COLUMBIA UNIVERSITY NEW YORK	0		96,700
CORNELL UNIVERSITY MEDICAL CENTER	0		28,308
DARTMOUTH COLLEGE	0		34,159
DELAWARE STATE UNIVERSITY	228,543		0
EMORY UNIVERSITY	0		47,563
FED. OF AM. SOC. FOR EXPER BIOLOGY	113,534		0
FLORIDA AGRI. & MECH. U.	197,068		0
FLORIDA INSTITUTE OF TECHNOLOGY	0		22,328
FORT LEWIS COLLEGE	112,333		0
HAMPTON UNIVERSITY	514,527		0
HARVARD UNIVERSITY	0		101,632
HEALTH SCIENCE CENTER AT BROOKLYN	0		20,736
HERBERT H. LEHMAN COLLEGE	115,100		0
HOWARD UNIVERSITY	306,375		15,508
HUMACAO UNIVERSITY COLLEGE	147,552		0
HUNTER COLLEGE	194,888		0
INTER AM. U. OF PUERTO RICO	85,563		23,910
JACKSON STATE UNIVERSITY	235,247		0
JOHNS HOPKINS UNIVERSITY	0		123,262
JOHNSON C. SMITH UNIVERSITY	99,156		0
LINCOLN UNIVERSITY	169,292		0
MASSACHUSETTS INS. OF TECHNOLOGY	0		39,743
MEHARRY MEDICAL COLLEGE	0		27,359
MONTANA STATE UNIVERSITY	11,847		0
MOREHOUSE SCHOOL OF MEDICINE	0	$225,305	28,054
MORGAN STATE UNIVERSITY	352,445		0
MOUNT SINAI SCHOOL OF MEDICINE	0		29,849
MOUNT ST. MARY'S COLLEGE	237,295		0
NEW MEXICO ST. U. LAS CRUCES	219,363		0
NEW YORK UNIVERSITY	0		35,978
N. CAR. AGRI & TECH ST. U.	232,566		0
NORTH CAROLINA CENTRAL U.	291,081		0
N. CAR. ST. U. RALEIGH	0		25,488
NORTHERN U. MEDICAL SCHOOL	62,035		0

INSTITUTION	INSTITUTION SUPPORT	OTHER RESEARCH	INDIVIDUAL SUPPORT
NORTHWESTERN UNIVERSITY	0		30,844
OHIO STATE UNIVERSITY	0		26,784
PA. STATE U.-UNIV PARK	0		20,449
PONTIFICAL CATH. U. OF PR	183,743		0
PRINCETON UNIVERSITY	0		3,002
PURDUE U. WEST LAFAYETTE	0		110,721
RUST COLLEGE	196,341		0
SAN DIEGO ST. UNIV.	205,952		0
SAN JOSE STATE UNIV.	184,796		0
SAVANNAH STATE COLLEGE	177,539		0
SOC. FOR THE ADV.CHICANOS/NAT AM	178,254		0
SOCIETY OF TOXICOLOGY	28,267		0
STANFORD UNIVERSITY	0		11,712
STILLMAN COLLEGE	134,779		0
ST. MARY'S UNIVERSITY	251,975		0
TALLADEGA COLLEGE	321,967		0
TENNESSEE STATE UNIVERSITY	178,281		0
TEXAS SOUTHERN UNIVERSITY	139,622		0
TOUGALOO COLLEGE	271,884		0
TUSKEGEE UNIVERSITY	153,175		0
U. OF ALABAMA AT BIRMINGHAM	0		16,308
U. OF ALABAMA IN HUNTSVILLE	108,505		0
U. OF ARKANSAS AT PINE BLUFF	154,645		0
U. OF CALIFORNIA, SANTA CRUZ	0		17,307
U. OF CALIFORNIA DAVIS	0		32,610
U. OF CALIFORNIA IRVINE	0		17,090
U. OF CALIFORNIA LOS ANGELES	0		16,404
U. OF CALIFORNIA RIVERSIDE	0		16,838
U. OF CALIFORNIA SAN DIEGO	0		55,807
U. OF CALIFORNIA SAN FRANCISCO	0		19,255
U. OF CALIFORNIA SANTA CRUZ	165,859		0
UNIVERSITY OF CHICAGO	0		41,685
UNIV. OF HAWAII AT MANOA	157,356		0
U. OF ILLINOIS URBANA-CHAMPAIGN	0		25,974
U. OF MARYLAND BALT PROF SCHOOL	0		30,567
U. OF MARYLAND COLLEGE PK CAMPUS	0		17,841
U. OF MARYLAND EASTERN SHORE	121,833		0
UNIVERSITY OF MIAMI	0		38,934
U. OF MICHIGAN AT ANN ARBOR	0		39,017
UNIVERSITY OF NORTH DAKOTA	123,146		0
UNIVERSITY OF PENNSYLVANIA	0		53,865
U. OF PUERTO RICO MAYAGUEZ	242,438		0
U. OF PUERTO RICO MED SCIENCES	0		29,770
U. OF PUERTO RICO RIO PIEDRAS	378,045		23,400
UNIVERSITY OF TEXAS EL PASO	173,886		0
U. OF TEXAS MD ANDERSON CAN CTR	0		13,074
U. OF TEXAS SAN ANTONIO	236,314		12,776
U. OF THE DISTRICT OF COLUMBIA	109,604		0
U. OF THE VIRGIN ISLANDS	151,558		0
U. OF WISCONSIN AT MADISON	0		25,371
VIRGINIA COMMONWEALTH UNIV.	0		17,309
VIRGINIA STATE UNIVERSITY	0		35,300
VIRGINIA UNION UNIVERSITY	184,860		0

INSTITUTION	INSTITUTION SUPPORT	OTHER RESEARCH	INDIVIDUAL SUPPORT
WAYNE STATE UNIVERSITY	173,018		0
WINSTON-SALEM STATE UNIV	126,419		0
XAVIER UNIV. OF LOUISIANA	322,235		0
YALE UNIVERSITY	0		92,002
YESHIVA UNIVERSITY	0		127,792
YORK COLLEGE	224,096		0
TOTAL	$13,343,504	$225,305	$1,938,733

Mr. Stokes: Please provide the amount of MARC funds awarded to Historically Black Colleges and Universities (HBCUs), and the percentage of total MARC funds awarded to HBCUs.

Dr. Cassman: The amount of MARC funds awarded to HBCUs in FY 1994 was $7,504,977. This amount represents 48.4 percent of the total MARC funds awarded in FY 1994.

Mr. Stokes: Please provide the amount of MARC funds awarded to non-minority institutions, and the percentage of total MARC funds awarded.

Dr. Cassman: The amount of MARC funds awarded to non-HBCUs in FY 1994 was $8,002,565. This amount represents 51.6 percent of the total MARC funds awarded in FY 1994.

MINORITY BIOMEDICAL RESEARCH SUPPORT (MBRS) FUNDING

Mr. Stokes: Please provide the amount of MBRS funding awarded by institution.

Dr. Cassman: The following table reflects the Fiscal Year 1994 MBRS funding by institution:

INSTITUTION	SUPPORT
ALABAMA AGRI AND MECH UNIVERSITY	$299,792
ALABAMA STATE UNIVERSITY	367,559
ALBANY STATE COLLEGE	296,329
ALCORN STATE UNIVERSITY	155,333
BARRY UNIVERSITY	339,267
BENEDICT COLLEGE	314,077
BENNETT COLLEGE	206,633
BETHUNE-COOKMAN COLLEGE	293,577
BRONX COMMUNITY COLLEGE	346,680
CALIFORNIA STATE UNIVERSITY HAYWARD	417,396
CALIFORNIA STATE UNIVERSITY LONG BEACH	538,893
CALIFORNIA STATE UNIVERSITY LOS ANGELES	1,691,938
CALIFORNIA STATE UNIVERSITY NORTHRIDGE	541,634
CALIFORNIA STATE UNIV-DOMINGUEZ HILLS	318,289
CAL. STATE U. FULLERTON	147,809
CAYEY UNIVERSITY COLLEGE	268,749
CENTRAL UNIVERSITY OF THE CARIBE	529,204
CHAMINADE UNIVERSITY OF HONOLULU	303,193
CHARLES R. DREW UNIVERSITY OF MED & SCI	412,975

INSTITUTION	SUPPORT
CHICAGO STATE UNIVERSITY	986,954
CLARK ATLANTA UNIVERSITY	1,116,481
COLLEGE AT OLD WESTBURY	451,405
COPPIN STATE COLLEGE	200,277
CUNY	506,170
DELAWARE STATE UNIVERSITY	448,809
EAST LOS ANGELES COLLEGE	387,812
ELIZABETH CITY STATE UNIVERSITY	119,100
FAYETTEVILLE STATE UNIVERSITY	492,753
FISK UNIVERSITY	383,316
FLORIDA AGRI. & MECH. UNIVERSITY	762,455
FLORIDA INTERNATIONAL	591,140
GRAMBLING STATE UNIVERSITY	257,686
HERBERT H. LEHMAN COLLEGE	709,988
HOWARD UNIVERSITY	2,372,606
HUMACAO UNIVERSITY COLLEGE	428,811
HUNTER COLLEGE	526,008
INTER AMERICAN UNIVERSITY OF PUERTO RICO	177,624
JACKSON STATE UNIVERSITY	492,221
JARVIS CHRISTIAN COLLEGE	122,889
JOHNSON C. SMITH UNIVERSITY	262,887
KENTUCKY STATE UNIVERSITY	170,034
LANE COLLEGE	77,713
LINCOLN UNIVERSITY	224,274
MEHARRY MEDICAL COLLEGE	1,380,728
MONTANA STATE UNIVERSITY	287,034
MOREHOUSE COLLEGE	517,748
MOREHOUSE SCHOOL OF MEDICINE	1,223,053
MORRIS COLLEGE	64,988
NAVAJO COMMUNITY COLLEGE	129,605
NEW MEXICO HIGHLANDS UNIVERSITY	229,899
NEW MEXICO STATE UNIVERSITY LAS CRUCES	776,355
NORFOLK STATE UNIVERSITY	256,737
NORTH CAROLINA AGRI & TECH ST UNIV	550,721
NORTH CAROLINA CENTRAL U.	657,492
NORTHERN ARIZONA	235,923
OAKWOOD COLLEGE	184,122
PHILANDER SMITH COLLEGE	154,742
PONCE SCHOOL OF MEDICINE	1,004,552
PRAIRIE VIEW AGRI & MECH UNIVERSITY	485,321
RUST COLLEGE	179,309
RUTGERS THE STATE UNIV NEW BRUNSWICK	620,492
SAN DIEGO STATE UNIVERSITY	336,319
SAN JOSE STATE UNIVERSITY	975,642
SELMA UNIVERSITY	264,492
SOUTH CAROLINA STATE UNIVERSITY	183,103
SOUTHEASTERN OKLAHOMA STATE UNIVERSITY	204,727
SOUTHERN UNIVERSITY SHREVEPORT-BOSSIER	135,679
SPELMAN COLLEGE	631,277
STILLMAN COLLEGE	180,158
ST. JOHN'S UNIVERSITY	352,218
ST. PAUL'S COLLEGE	192,899
TALLADEGA COLLEGE	118,121
TENNESSEE STATE UNIVERSITY	210,841

INSTITUTION	SUPPORT
TEXAS SOUTHERN UNIVERSITY	532,083
TEXAS WOMAN'S UNIVERSITY	329,125
TOUGALOO COLLEGE	216,097
TUSKEGEE UNIVERSITY	500,389
UNIVERSITY OF NEW MEXICO	673,753
UNIVERSITY OF ARKANSAS AT PINE BLUFF	441,294
UNIVERSITY OF CALIFORNIA SAN DIEGO	245,840
UNIVERSITY OF CALIFORNIA SANTA CRUZ	416,397
UNIVERSITY OF GUAM	484,272
UNIVERSITY OF HAWAII AT HILO	602,821
UNIVERSITY OF HAWAII AT MANOA	290,644
UNIVERSITY OF PUERTO RICO MAYAGUEZ	511,093
UNIVERSITY OF PUERTO RICO MED SCIENCES	1,199,435
UNIVERSITY OF PUERTO RICO RIO PIEDRAS	1,543,021
UNIVERSITY OF SOUTHERN COLORADO	586,746
UNIVERSITY OF TEXAS EL PASO	965,312
UNIVERSITY OF TEXAS SAN ANTONIO	1,100,293
UNIVERSITY OF TEXAS-PAN AMERICAN	475,560
UNIVERSITY OF THE DISTRICT OF COLUMBIA	601,304
UNIVERSITY OF THE VIRGIN ISLANDS	312,798
VIRGINIA STATE UNIVERSITY	205,989
WAYNE STATE UNIVERSITY	1,066,729
WINSTON-SALEM STATE UNIVERSITY	458,509
XAVIER UNIVERSITY OF LOUISIANA	558,483
YORK COLLEGE	941,443
TOTAL	$48,042,467

Mr. Stokes: Please provide the amount of MBRS funds awarded to Historically Black Colleges and Universities (HBCUs), and the percentage of total MBRS funds awarded to HBCUs.

Dr. Cassman: The amount of MBRS funds awarded to HBCUs in FY 1994 was $20,935,455. This amount represents 43.6 percent of the total MBRS funds awarded in FY 1994.

Mr. Stokes: Please provide the amount of MBRS funds awarded to non-minority institutions, and the percentage of total MBRS funds awarded.

Dr. Cassman: The amount of MBRS funds awarded to non-HBCUs in FY 1994 was $27,107,012. This amount represents 56.4 percent of the total MBRS funds awarded in FY 1994.

NRSA TRAINING LEVELS

Ms. Lowey: I am very interested in NIGMS's work in training individuals to meet personnel shortaged in expanding fields of science. How do you determine which fields are experiencing a shortage of personnel -- with enough advance warning that you aren't training people for fields that are no longer expanding?

Dr. Cassman: The NIH relies on the National Academy of Science (NAS) to provide advice on research training fields, as is mandated by the National Research Service Award (NRSA) authorizing legislation. Every four years, the Academy organizes a select committee of experts from academia and industry to conduct studies and to recommend both policy changes and training support levels. Over the past 20 years, these committees have made recommendations broken out for broad research areas, instead of for specific fields, citing the advantages of such multidisciplinary research training and the large extent of research field mobility that occurs. In their recent (June, 1994) report, the NAS committee recommended no substantial changes in the overall NRSA training levels. In making this recommendation, the committee pointed out: the lack of evidence of underemployment or unemployment in biomedical fields, the high quality of the trainees, and the major contribution these relatively small NRSA programs make to biomedical research training.

NIGMS SUPPORTED BREAST CANCER RESEARCH AND RESEARCH TRAINING

Ms. Lowey: Your justification states that you will fund research and research training in the field of breast cancer -- as well as women's health. Could you elaborate on what will be done in these areas?

Dr. Cassman: Research - Prevention, early diagnosis and effective treatment of breast cancer requires a basic understanding of predisposing susceptibility factors, the cellular processes that operate in uncontrolled growth of breast tissue, and the mechanisms that promote tumor cell metastasis. Virtually every aspect of normal cell structure and function must be understood in order to comprehend what goes awry during the transformation of a normal cell to a cancerous one. NIGMS supports fundamental research in cell biology, biochemistry, chemistry, pharmacology, molecular biophysics, genetics, molecular biology and physiology that impacts on virtually all areas of breast cancer research, by providing this basic understanding. Furthermore, research on the chemistry and synthesis of natural products, and on the molecular structure of biologically active compounds, provides the foundation for the development of drugs used in the treatment of breast cancer. NIGMS currently is actively supporting research in many areas relevant to breast cancer, including:

Cell division - Studies on the molecules and genes that regulate the cycle of normal cell growth and division. These genes and molecules are prime targets for cancer therapy.

Programmed Cell Death - Studies on the factors that direct a cell to die, rather than to grow and divide. Some tumor suppressor genes activate programmed cell death and are targets for anti-cancer therapy.

Cell adhesion - Changes in expression of adhesion molecules that determine how cancer cells invade and metastasize to new sites.

Cell motility - The cytoskeleton structure of a cell that determines cell division and motility. Drugs, such as taxol, interfere with the cytoskeleton and can prevent uncontrolled cell division and metastasis.

Chemistry and pharmacology - Purification and synthesis of natural plant and animal products that are a source of bioactive, anti-tumor agents.

Structural biology - Research on the structure and function of receptors, growth factors, DNA transcription factors and key enzymes of the cell cycle that provide strategies for understanding, treating and preventing cancers.

Imaging techniques - Spectroscopic techniques, design of molecular probes and imaging methods for earlier and more sensitive detection of cancer.

Genetics - Studies of genes that are tumor-promoting or tumor-suppressing when inappropriately expressed and are targets for gene therapy.

DNA repair - Research on DNA repair genes and enzymes that may lead to the design of new anti-cancer drugs.

Angiogenesis - Research on wound repair that provides knowledge of growth factors and cytokines that promote blood vessel growth (angiogenesis) correlated with tumor invasion and metastasis.

Research Training - NIGMS supports interdisciplinary predoctoral training in the areas of: Cellular and Molecular Biology and Biochemistry; Genetics; Structural Biology; Pharmacological Sciences; Biotechnology; and the Chemistry/Biology Interface. NIGMS also supports the Medical Scientist Training Program (MSTP) for M.D./Ph.D students. The trainees supported by these programs account for approximately one half of all predoctoral trainees supported by the NIH. NIGMS is the sole Institute with an MSTP training program. These programs train future scientists in all the basic areas described above, and therefore contribute to the pool of scientists that will make breakthroughs related to breast cancer. The MSTP program uniquely positions scientists to apply basic knowledge to clinical diseases.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

FY 1996 Budget — Page No.

Organization chart 126

Appropriation language 127

Amounts available for obligation 129

Budget mechanism table 130

Summary of changes 132

Budget authority by object 134

Administrative costs 136

Authorizing legislation 137

Appropriation history 138

Budget authority by activity 140

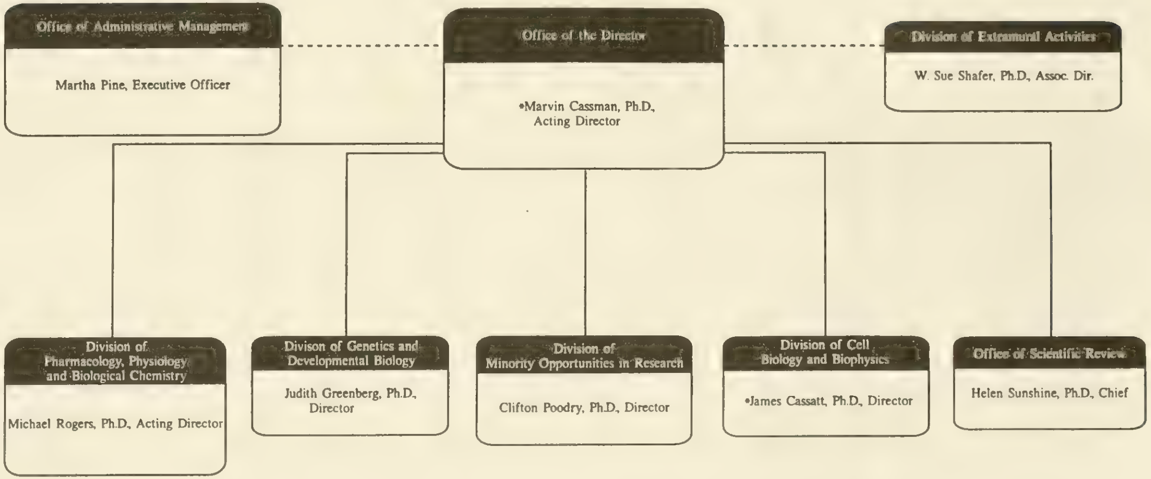
Justification:

- A. General statement 143
- B. Extramural research 146
- C. Intramural research 156
- D. Research management and support 158
- E. Detail of full-time equivalent employment (FTE) 160
- F. Detail of end-of-year employment 161

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

National Institute Of General Medical Sciences

Organization Structure


Office of Administrative Management
Martha Pine, Executive Officer
Office of the Director
•Marvin Cassman, Ph.D., Acting Director
Division of Extramural Activities
W. Sue Shafer, Ph.D., Assoc. Dir.
Division of Pharmacology, Physiology and Biological Chemistry
Michael Rogers, Ph.D., Acting Director
Divison of Genetics and Developmental Biology
Judith Greenberg, Ph.D., Director
Division of Minority Opportunities in Research
Clifton Poodry, Ph.D., Director
Division of Cell Biology and Biophysics
•James Cassatt, Ph.D., Director
Office of Scientific Review
Helen Sunshine, Ph.D., Chief

January 1995 • Filling more than one position

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and Title IV of the Public Health Service Act with respect to general medical sciences, [$877,113,000] *$907,674,000*.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation	$875,511,000	$877,113,000	$907,674,000
Section 205 Procurement reduction	---	-94,000	---
Section 207 Rent reduction	---	-9,000	---
Section 513 S&E reduction.	---	-124,000	---
Subtotal, adjusted appropriation	875,511,000	876,886,000	907,674,000
Real transfer from:			
Office of the Director, NIH for MARC and MBRS	---	+3,375,000	---
Comparative transfer to:			
Office of AIDS research, NIH for HIV activities	-23,943,000	---	---
Subtotal, adjusted budget authority	851,568,000	880,261,000	907,674,000
Unobligated balance lapsing	-16,000	---	---
Total, Obligations	851,552,000	880,261,000	907,674,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994--$15,033,000; FY 1995--$20,000,000; FY 1996--$20,000,000.

Also excludes funding for HIV activities: FY 1995--$24,664,000; FY 1996--$26,135,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	2,510	$519,878,000	2,159	$459,087,000	2,422	$528,401,000
Admin. supplemental	(39)	1,264,000	(120)	1,122,000	(120)	1,169,000
Competing						
Renewal	408	93,447,000	657	153,666,000	413	103,389,000
New	332	53,937,000	425	70,562,000	405	72,403,000
Supplemental	9	1,107,000	14	1,686,000	11	1,427,000
Subtotal, competing	749	148,491,000	1,096	225,914,000	829	177,219,000
Subtotal	3,259	669,633,000	3,255	686,123,000	3,251	706,789,000
SBIR/STTR	81	11,163,000	71	15,587,000	74	16,329,000
Subtotal, Research projects	3,340	680,796,000	3,326	701,710,000	3,325	723,118,000
Research Centers	8	6,952,000	9	8,389,000	9	8,389,000
Other research						
Research career program	15	950,000	20	1,306,000	27	1,763,000
MBRS	99	34,795,000	103	37,105,000	103	38,181,000
Other	71	3,731,000	85	4,000,000	97	4,700,000
Subtotal, other research	185	39,476,000	208	42,411,000	227	44,644,000
Total, research grants	3,533	727,224,000	3,543	752,510,000	3,561	776,151,000

Training:						
Individual awards						
Noncompeting	341	8,459,000	459	11,674,000	412	10,654,000
Competeting	269	6,674,000	182	4,540,000	229	6,057,000
Subtotal, individual	610	15,133,000	641	16,214,000	641	16,711,000
Institutional awards						
Noncompeting	2,946	66,614,000	2,273	51,535,000	2,970	69,301,000
Competing	519	12,853,000	1,287	28,503,000	590	13,268,000
Subtotal, institutional	3,465	79,467,000	3,560	80,038,000	3,560	82,569,000
Total, training	4,075	94,600,000	4,201	96,252,000	4,201	99,280,000
Research and development contracts	5	2,763,000	8	3,462,000	8	3,572,000
	FTEs		FTEs		FTEs	
Intramural research	18	1,136,000	16	1,105,000	14	1,010,000
Research management and support	161	25,845,000	166	26,932,000	165	27,661,000
TOTAL	179	851,568,000	182	880,261,000	179	907,674,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

132

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Summary of Changes

1995 Estimated budget authority	$880,261,000
1996 Estimated budget authority	907,674,000
Net change	+27,413,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increases		$782,000		+$12,000
b. Annualization of pay raise		782,000		+6,000
c. One more day of pay		782,000		+3,000
d. FY 1996 pay increase		782,000		+14,000
e. Centrally furnished services		281,000		−23,000
f. Inflationary increase		42,000		+1,000
Subtotal				+13,000
2. Research Management & Support				
a. Within grade increases		9,998,000		+145,000
b. Annualization of pay raise		9,998,000		+80,000
c. One more day of pay		9,998,000		+38,000
d. FY 1996 pay increase		9,998,000		+165,000
e. Centrally furnished services		7,418,000		+525,000
f. FECF unemployment compensation		9,998,000		+2,000
g. Service and supply fund increase		4,965,000		+170,000
h. Inflationary increase		3,763,000		+137,000
i. FTS reduction		75,000		−22,000
j. Working capital fund reduction		713,000		−19,000
Subtotal				+1,221,000
B. Program:				
1. Research projects grants:				
a. Noncompeting	2,159	460,209,000	+263	+69,361,000
b. Competing	1,096	225,914,000	−267	−48,695,000
c. SBIR/STTR	71	15,587,000	+3	+742,000
Subtotal	3,326	701,710,000	−1	+21,408,000

	No.	Amount	No.	Amount
3. Other Research:				
a. Research career program...........	20	1,306,000	+7	+457,000
b. MBRS program...........................	103	37,105,000	---	+1,076,000
c. Other research............................	85	4,000,000	+12	+700,000
Subtotal..	208	42,411,000	+19	+2,233,000
	FTTP			FTTP
4. Training...	4,201	96,252,000	---	+3,028 000
5. Research and development contracts..	8	3,462,000	---	+110,000
	FTE		FTE	
6. Intramural..	16	1,105,000	−2	−108,000
7. Research Management & Support.	166	26,932,000	−1	−492,000
Total changes..............................			−3	+27,413,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

134

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full–time equivalent employment.....	182	179	–3
Full–time equivalent of overtime and holiday hours..............	1	1	---
Average SES salary..............................	$107,379	$109,097	+$1,718
Average GS grade................................	9.8	9.8	---
Average GS salary................................	$36,876	$37,466	+$590
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)......	50,708	51,519	+811
Average salary of ungraded positions.	35,288	35,870	+582
Personnel compensation:			
Full–time permanent.........................	$7,731,000	$7,949,000	+$218,000
Other than full–time permanent........	892,000	914,000	+ 22,000
Other personnel compensation.........	282,000	290,000	+8,000
Special personal services payments.	3,000	3,000	---
Subtotal, personnel compensation.	8,908,000	9,156,000	+248,000
Personnel benefits................................	1,864,000	1,914,000	+50,000
Benefits for former personnel...............	8,000	8,000	---
Travel and transportation of persons...	272,000	272,000	---
Transportation of things.......................	55,000	55,000	---

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object – continued

	1995 Appropriation	1996 Estimate	Increase or Decrease
Rental payments to others	12,000	12,000	---
Communications, utilities, and miscellaneous charges	421,000	399,000	−22,000
Printing and reproduction	418,000	418,000	---
Other services:			
Consulting services	371,000	371,000	---
Other services	718,000	720,000	+2,000
Purchases from govt. accts	14,781,000	15,137,000	+356,000
R&D contracts	2,987,000	3,097,000	+110,000
Supplies and materials	133,000	133,000	---
Equipment	507,000	507,000	---
Grants, subsidies, and contributions	848,762,000	875,431,000	+26,669,000
Insurance Claim & Indemnities	44,000	44,000	---
Total Budget Authority by Object	880,261,000	907,674,000	+27,413,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

136

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Administrative Costs

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Personnel compensation:			
Full-time permanent (11.1)...............	$7,731,000	$7,949,000	+$218,000
Other than full-time permanent (11.3)............................	892,000	914,000	+22,000
Other personnel compensation (11.5).......................	282,000	290,000	+8,000
Special personnel services payments (11.8)..............................	3,000	3,000	---
Total, personnel compensation (11.9)......................	8,908,000	9,156,000	+248,000
Civilian personnel benefits (12.1).........	1,864,000	1,914,000	+50,000
Benefits for former personnel (13.0)....	8,000	8,000	---
Travel (21.0)...	272,000	272,000	---
Transportation of things (22.0).............	55,000	55,000	---
Rental payments to others (23.2).........	12,000	12,000	---
Communications, utilities, and miscellaneous charges (23.3).............	421,000	399,000	-22,000
Printing and reproduction (24.0)..........	418,000	418,000	---
Other services:			
Consulting services (25.1)..................	371,000	371,000	---
Other services (25.2)..........................	718,000	720,000	+2,000
Purchases from govt. accts (25.3)....	9,907,000	10,263,000	+356,000
Supplies and Materials (26.0)..............	133,000	133,000	---
Total..	23,087,000	23,721,000	+634,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation................	Section 301	42 §241	Indefinite		Indefinite	
National Institute of General Medical Sciences......................	Title IV, Part C	42 §285	Such sums as necessary	$784,009,000	Indefinite	$808,394,000
National Research Service Awards...........	Section 487 (D)	42 §288	Such sums as necessary	96,252,000	such sums as necessary	99,280,000
Total Budget Authority.				880,261,000		907,674,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$471,533,000	$576,562,000	$565,271,000	$570,916,000
1988	482,004,000	666,037,000 2/	650,617,000	632,676,000
1989	676,728,000 3/	623,087,000 4/5/	690,653,000 4/	690,653,000
1990	766,421,000 6/	692,639,000 7/	752,939,000 8/	691,278,000 9/
1990 Sequester	---	---	---	–9,496,000
1991	745,494,000 7/	693,499,000 10/7/	779,351,000 7/	760,010,000 11/
1991 Sequester	---	---	---	(10,000)
1992	833,180,000	820,160,000	815,158,000	818,910,000 12/
1993	862,069,000	833,807,000	824,529,000	832,581,000 13/
1994	833,064,000	875,511,000	875,511,000	875,511,000
1995 14/	882,189,000	877,113,000	877,113,000	876,886,000 15/
1996 14/	907,674,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ Does not include funding for AIDS research ($11,100,000). Proposed for consolidation at the Office of the Assistant Secretary for Health.

4/ Includes $11,100,000 for AIDS research.

5/ Excludes $69,841,000 in NRSA training programs not considered.

6/ Excludes funds for AIDS research proposed for consolidation in the Office of the Assistant Secretary for Health. Includes funds for the Human Genome Research Initiative.

7/ Includes funds for AIDS research and the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources. Excludes funds for the Human Genome Research Initiative to be considered under a separate new appropriation account.

8/ Includes funds for AIDS research and funds for the Human Genome Research Initiative.

9/ Includes funds for AIDS research. Excludes funds for the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources, the Human Genome Research Initiative and an enacted administrative reduction of $588,000.

10/ Excludes $85,650,000 in NRSA training programs not considered.

11/ Excludes enacted administrative reductions of $19,240,000 and funds transferred from other accounts for the Shannon awards.

12/ Excludes enacted administrative reductions of $1,276,000 and a rescission of $790,000.

13/ Excludes enacted administrative reductions of $7,224,000.

14/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

15/ Excludes enacted administrative reductions of $94,000, $9,000, and $124,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Estimate		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural research												
Genetics and developmental biology	---	$249,704	---	$255,541	---	$265,578	---	$277,204	---	$285,441	---	+$8,237
Pharmacology, Physiology and Biological Chemistry	---	240,980	---	246,613	---	257,152	---	260,279	---	267,179	---	+6,900
Cell Biology and Biophysics	---	233,495	---	238,953	---	248,708	---	256,796	---	264,505	---	+7,709
Minority opportunities in research:												
Minority biomedical research support	---	33,190	---	32,795	---	34,795	---	37,105	---	38,181	---	+1,076

Minority access to research careers	---	13,514	---	13,103	---	14,786	---	16,653	---	18,235	---	+1,582
Special minority initiatives	---	1,617	---	1,856	---	3,568	---	4,187	---	5,462	---	+1,275
Subtotal	---	48,321	---	47,754	---	53,149	---	57,945	---	61,878	---	+3,933
Subtotal, extramural research	---	772,500	---	788,861	---	824,587	---	852,224	---	879,003	---	+26,779
Intramural research	19	1,109	19	1,176	18	1,136	16	1,105	14	1,010	-2	-95
Research management and support	173	24,950	172	25,304	161	25,829	166	26,932	165	27,661	-1	+729
Total Obligations	192	798,559	191	815,341	179	851,552	182	880,261	179	907,674	-3	+27,413
Unobligated balance lapsing		47		44		16		---		---		---
Total, Budget Authority	192	798,606	191	815,385	179	851,568	182	880,261	179	907,674	-3	+27,413

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of General Medical Sciences

FY 1994 Actual		FY 1995 Estimate		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
179	$851,568,000	182	$880,261,000	179	$907,674,000	-3	+$27,413,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute of General Medical Sciences (NIGMS). Justification of NIGMS FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

In FY 1996, NIGMS will continue to support basic research that is not targeted to specific diseases, organs, life stages, or environmental factors. This support largely takes the form of investigator-initiated grants in biomedical areas where the need for knowledge is most critical. Last year's accomplishments are described in this budget request because they exemplify the research NIGMS funds and pave the way for new grant applications.

NIGMS grantees use the approaches of structural biology, biophysics, genetics, cell and molecular biology, biochemistry, chemistry, and pharmacology to improve our understanding of fundamental life processes. The results of this research have broad applications in many areas, including disease treatment, diagnosis, and prevention. Other payoffs of NIGMS-supported research include new knowledge, concepts, tools, and techniques that are used by scientists in academia and industry. NIGMS also helps industry meet its needs for a continued supply of newly trained personnel.

In these ways, basic research findings fuel the growth of the biotechnology and pharmaceutical industries, helping to maintain the United States' position as a world leader in these sectors. At a 1985 meeting of the advisory committee to the NIH director, representatives of the biotechnology industry were asked what NIH could do to help them the most, and their answer was: support basic research. This recommendation was reinforced by a 1991 survey of biotechnology companies, which overwhelmingly identified additional research as the industry's "number one need." According to the report on this survey, "this finding is a ringing affirmation of the criticality of government-sponsored research, which stems primarily from the NIH."

Nobel Prizes: Over the years, NIGMS grantees have received a substantial number of Nobel Prizes in physiology or medicine and chemistry. This trend--which underscores the significance of the basic research the Institute supports--continued in 1994, when two more Institute grantees received Nobel Prizes.

Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center at Dallas shared the Nobel Prize in physiology or medicine for his work on G proteins, key components of the communication system that regulates cellular activity. NIGMS has supported Dr. Gilman's research since 1985, and also supported his pre- and postdoctoral research training.

The Nobel Prize in chemistry went to Dr. George A. Olah of the University of Southern California, who received over $4 million in research grant support from NIGMS between 1967 and 1993. Dr. Olah's work focuses on the structure and function of highly reactive organic molecules that are involved in natural and synthetic chemical processes. The reagents and methods Dr. Olah developed are used today in the chemical synthesis of a wide variety of materials, from gasoline to pharmaceuticals. His work also contributed to the understanding of enzyme reaction mechanisms in a broad range of physiological processes.

The President's appropriation request of $907,674,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NIGMS during the last 5 years has been as follows:

	Amount	FTE
FY 1991	$742,221,000	184
FY 1992	798,606,000	192
FY 1993	815,385,000	191
FY 1994	851,568,000	179
FY 1995	880,261,000	182

Purpose and Method of Operation

NIGMS places major emphasis on the support of individual, investigator-initiated research grants. It funds a limited number of research centers in selected fields--such as trauma and burn injury research and the pharmacological sciences (including anesthesiology)--in which the interaction of basic and clinical researchers is critical for rapid scientific progress.

NIGMS also funds research contracts that provide important resources for basic scientists. In research training, the Institute supports a large portfolio of both individual fellowship awards and institutional training grants. Some of these training programs help meet personnel shortages in rapidly expanding fields of science, such as biotechnology, or promote the access of individuals from minority groups to biomedical research careers.

Overall Budget Policy

The NIGMS budget request for FY 1996 continues to emphasize basic biomedical research studies through the support of investigator-initiated research project grants. The budget request is $907,674,000, an increase of $27,413,000 or 3.1 percent over the FY 1995 estimate. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting components, grant awards received an average 4 percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one-time non-recurring costs, such as equipment.

The request will support 829 competing research project grants, 2,422 noncompeting research project grants, and 74 small business awards. The FY 1996 budget request will fund 9 research centers, 27 research career awards, 103 Minority Biomedical Research Support awards, 97 other research projects, and 8 research and development contracts. This represents the same number of research centers, Minority Biomedical Research Support awards, and research and development contracts that were funded in FY 1995; and an increase of 3 small business awards, 7 research career awards, and 12 other research projects over FY 1995. Approximately 4,201 research trainees will be supported in FY 1996, the same level as in FY 1995.

In FY 1996, NIGMS will fund research and/or research training in the following special initiative areas: AIDS, breast cancer, mutations and environmental cancers, women's health, disorders of development and reproductive biology, DNA sequencing technology, structural biology and drug design, tuberculosis, and minority health.

Included in this request are full-time equivalent (FTE) reductions for both Intramural Research and Research Management and Support. The request will provide 179 FTEs, a decrease of 3 FTEs from the FY 1995 level.

EXTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Estimate	FY 1996 Estimate	Increase or Decrease
$824,587,000	$852,224,000	$879,003,000	+$26,779,000

Rationale for the Budget Request

The FY 1996 budget estimate for the Extramural Programs is $879,003,000, an increase of 3.1 percent over the FY 1995 estimate of $852,224,000. Funding for the Extramural Programs during the last 5 years has been as follows:

	Amount
FY 1991	$718,513,000
FY 1992	772,500,000
FY 1993	788,861,000
FY 1994	824,587,000
FY 1995	852,224,000

With the FY 1996 extramural request these funds will provide support for the following activities: the Division of Genetics and Developmental Biology, $285,441,000, an increase of $8,237,000 or 3% over the FY 1995 estimate of $277,204,000, the Division of Pharmacology, Physiology, and Biological Chemistry, $267,179,000, an increase of $6,900,000 or 2.7% over the FY 1995 estimate of $260,279,000, the Division of Cell Biology and Biophysics, $264,505,000, an increase of $7,709,000 or 3% over the FY 1995 estimate of $256,796,000, and the Division of Minority Opportunities in Research, $61,878,000, and increase of $3,933,000 or 6.8% over the FY 1995 estimate of $57,945,000.

DIVISION OF GENETICS AND DEVELOPMENTAL BIOLOGY

This division supports basic research that will yield a better understanding of genetic processes and the mechanisms of inheritance in health and disease. Much of this research examines the intricate machinery that translates genetic instructions contained in the DNA into the myriad of proteins that catalyze and carry out all life processes. Understanding this machinery on the most fundamental level provides scientists with many ways in which to intervene to diagnose, prevent, or treat diseases. The division also supports research in the areas of cell growth and development.

The following are examples of the research funded by the division:

Mouse Model for Hypertension: About 20 percent of adults in the United States have essential hypertension, making it a major health problem in this country. To facilitate studies of the genetic aspects of this complex disorder, Dr. Oliver Smithies of the University of North Carolina, Chapel Hill has produced a "knockout" mouse model for human hypertension. Knockout mice, which are engineered to contain modifications in specific genes, enable scientists to study exactly what a gene does within a living organism. Dr. Smithies has used his mouse model to demonstrate a direct causal relationship between the maintenance of blood pressure and the expression of two major regulatory molecules, angiotensinogen (AGT) and atrial natriuretic peptide (ANP). His work has established that mice with more copies of the gene for AGT have higher blood pressure and that reduced expression of ANP leads to salt-sensitive hypertension. The new model should greatly increase scien-tists' ability to study hypertension and to develop better ways to combat it.

Progress in Understanding Cell Cycle Control: In recent years, many details of the complex biochemical mechanisms involved in the cycle of cell growth and division have been discovered. This research is leading to an improved understanding of the specific role of oncogenes, which are directly involved in the development of cancer, and tumor suppressor genes, which are involved in cancer when their normal inhibitory functions are disrupted. For many years, Dr. David Beach of Cold Spring Harbor Laboratory has been in the forefront of cell cycle research. He has made enormous progress in understanding how specific proteins interact during the properly regulated cell cycle. He and other researchers have found this process to depend upon the highly complex control of two interacting families of proteins, cyclin-dependent kinases and cyclins. Pairs of these proteins regulate all stages of the cell cycle.

This year, a cell cycle protein called p16 and a close relative, p15, which were both described by Dr. Beach as inhibitors of specific pairs of cell cycle regulators, were identified by Dr. Beach and others as the products of possible tumor suppressor genes. Although researchers are still determining how important p15 and p16 are as tumor suppressors, the work is an important addition to the accumulating body of knowledge on the relationship between the cell cycle and cancer.

Understanding an Important Male Hormone: Basic research on the regulation of the synthesis of male hormones may have an unexpected payoff for pharmaceutical companies seeking to understand how drugs based on these hormones work. The male hormone dihydrotestosterone (DHT) plays a key role in the development of male sex characteristics. DHT is converted from another male hormone, testosterone, by the enzyme 5-ASR. Overabundance of DHT has been correlated with enlargement of the prostate in elderly men, and even with cancer of the prostate. Now, Dr. David Russell of the University of Texas Southwestern Medical Center at Dallas has shown that there are two forms of 5-ASR, Type I and Type II, which apparently have very different functions. Type II is localized in tissues that are involved in such conditions as male-pattern baldness, prostate enlargement, and abnormal hair growth in women. The Type I enzyme, on the other hand, is correlated with juvenile acne. These findings are providing powerful tools for understanding the mechanism of action of drugs, such as Proscar™, that are prescribed for prostate enlargement, and suggest approaches to the development of new therapeutic agents for conditions such as acne and male-pattern baldness.

Genetic Determinants of Behavior in Roundworms: There is growing evidence that, to some extent, behavior has genetic determinants, yet the exact relationship between specific genes and behaviors is largely unknown. In work that contributes to the enormously complex task of defining very simple behaviors at the molecular level, Dr. H. Robert Horvitz of MIT has shown that the roundworm C. elegans appears to have rudimentary senses that may correspond to smell and taste. He has determined that C. elegans uses different sets of neurons to sense volatile substances and soluble substances produced by its food, the E. coli bacterium. Dr. Horvitz has gone on to show that abnormalities in this "sensing" behavior are the result of defects in the genes for two neurotransmitters, serotonin and dopamine, which are known to be important in certain human behaviors such as depression, anxiety, and sleep.

Jellyfish Protein May Become Valuable Research Tool: As an offshoot of his work on nervous system development in roundworms, Dr. Martin Chalfie of Columbia University has developed a green fluorescent protein (GFP) for use as a biological tracer. Other techniques for tagging molecules exist but, unlike GFP, these tags can only be detected after the cells are killed. GFP, which comes from a bioluminescent jellyfish, allows scientists to watch genes turn on and off and to see where specific proteins go in living cells. Simple blue light is all GFP needs to stimulate the fluorescence. Dr. Chalfie anticipates that GFP may be useful for cell sorting, for studies of cell growth and migration, for selectively killing marked cells, and as a marker for determining the origin of specific tissues. Already, many in the research community have begun to employ GFP in various studies.

For example, another NIGMS grantee at Columbia, Dr. Tulle Hazelrigg, has used the GFP labeling technique to follow messenger RNA (which carries the genetic instructions for the manufacture of proteins) in developing fruit fly eggs. This work showed that a protein, called Exu, binds directly to the RNA. The bound complex is then transported along cellular organelles called microtubules and targeted to a specific part of the egg. The marker enabled Dr. Hazelrigg to demonstrate directly that the Exu protein interacts with microtubules, thereby increasing our understanding of cell differentiation during embryo formation.

DIVISION OF PHARMACOLOGY, PHYSIOLOGY, AND BIOLOGICAL CHEMISTRY

This division supports research ranging from the chemical synthesis of biologically important natural products to the elucidation of cellular signal transduction mechanisms that mediate drug action. This includes studies on the genetic and metabolic influences on drug effectiveness in humans and the mechanisms of action of local and general anesthetics. The goal of the research supported by the division is to expand our knowledge of how therapeutic substances work, especially the basic biological, chemical, and molecular processes that underlie drug action. These accomplishments help open new fields of investigation and also create opportunities for the development of new therapeutics. The division also supports research concerned with the examination of the body's response to trauma and burn injury.

The following are examples of the research funded by the division:

New Process for the Synthesis of Vitamin D Analogs: Dr. Barry M. Trost of Stanford University has recently patented a chemical reaction that may be useful in the synthesis of analogs (chemical variants) of vitamin D. Vitamin D is necessary to prevent defective bone mineralization, leading to severe deformities. But in order to perform its function in the body, vitamin D must be converted to an active analog. Individuals with kidney disease or certain genetic deficiencies are unable to utilize vitamin D even if they receive ample amounts. These individuals are treated with synthetic versions of the active analog, which are quite expensive.

Dr. Trost's reaction, which allows chemists to avoid side reactions during the synthesis of vitamin D and its analogs, will make it easier and less expensive to synthesize forms of the vitamin. More importantly, it will also help scientists learn more about the various biological effects of vitamin D, which may be useful in the treatment of diseases. Different forms of vitamin D may be useful in cancer chemotherapy, immunosuppression, and the treatment of osteoporosis and psoriasis. Dr. Trost's process is being considered for licensing and possible commercialization by two pharmaceutical companies.

Scientists Determine the First Structures of G Proteins: G proteins are part of a signaling system found in virtually all tissues and in animals from yeast to humans. These proteins, which are composed of several subunits, relay signals from extracellular substances like hormones and neurotransmitters to other intracellular proteins, which respond appropriately. G proteins are involved in functions such as thought, blood pressure control, cell growth and differentiation, the senses of smell and light detection, and the constellation of "fight or flight" responses to danger. Malfunctions of G proteins have been implicated in diseases such as hypertension, cardiac arrhythmias, asthma, cancer, and toxin-borne maladies such as whooping cough and cholera. In recognition of his extensive work on G proteins, NIGMS grantee Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center at Dallas shared the 1994 Nobel Prize in physiology or medicine.

NIGMS support of research on G proteins includes studies of their three-dimensional structures. The first detailed structures of the active and resting states of the alpha subunit of G proteins have been reported by Dr. Paul Sigler of Yale University (a grantee of the Division of Cell Biology and Biophysics) and Dr. Gilman. This work sheds light on how G proteins function.

Further knowledge of the shape and architecture of G proteins should yield clues as to how the alpha subunit interacts with the other subunits. The next step in the structural analysis of G proteins will be to learn precisely how their structure affects their interaction with various receptors and enzymes.

New Form of an Enzyme May Lead to Improved Drugs: Dr. Stephen J. Benkovic of Pennsylvania State University and his coworkers have discovered a novel form of an enzyme that is required for the replication of DNA--a step necessary for cell growth and division. The new form is distinguished from a known form of the enzyme in that it does not require a cofactor known as tetrahydrofolate and its mechanism of action and sensitivity to inhibitors are entirely different. The known form of the enzyme has been a mainstay of antibacterial and anticancer chemotherapy for many years. The discovery of a new form of the enzyme thus provides a target for the development of new types of drugs to fight bacterial diseases and cancer.

Anesthetics Interact with Specific Membrane Proteins: The anesthetics in use today can have a number of serious side effects, especially on the heart and lungs, rendering these drugs especially hazardous for elderly patients. Thus, researchers are particularly interested in developing new anesthetic drugs that have fewer side effects and are safer to use. Demonstration of specific sites on the cell surface membrane where anesthetics act offers the possibility that such new drugs can be designed and developed. In a step toward this goal, Dr. Neil Harrison of the University of Chicago has found evidence that implies that there are specific structural features in a type of cell membrane protein that interact directly with anesthetics. Exactly where and how the drugs interact with the protein is currently under intense investigation.

Another grantee, Dr. Nicholas Franks of Imperial College in London, has demonstrated that some types of cell membrane channels are much more sensitive to anesthetics than others. His work further supports the belief that anesthetics act directly on specific membrane proteins.

Tracking the Body's Response to Trauma: NIGMS grantees are making significant contributions to improving our understanding of how the body responds to trauma. A leader in this field is Dr. Richard Ulevitch of the Scripps Research Institute, who has focused on the role of an endotoxin called LPS in initiating septic shock. This endotoxin is a component of the cell walls of Gram-negative bacteria, including the *E. coli* that has contaminated some hamburger meat. Septic shock is characterized by fever, low blood pressure, reduced cardiac output, and often death. Dr. Ulevitch has pieced together the cascade of reactions following the release of LPS, and has identified points in the cascade at which therapeutic intervention might be possible. Most recently, Dr. Ulevitch and another NIGMS grantee at Scripps, Dr. Jiahuai Han, described a newly discovered enzyme in the cascade. This enzyme is a promising target for research that might lead to improved treatments for septic shock.

In related research, Drs. Timothy Billiar and Richard Simmons at the University of Pittsburgh have shown that nitric oxide, which has previously been found to play a role in many other body processes, is also involved in septic shock. Their work indicates that in response to trauma, the body overproduces nitric oxide to maintain blood flow and inhibit platelet aggregation. However, excessive overproduction of nitric oxide appears to cause some of the symptoms of septic shock. There is considerable interest in finding ways to inhibit the induction of nitric oxide in response to septic shock without preventing the synthesis of nitric oxide for its normal physiological functions.

DIVISION OF CELL BIOLOGY AND BIOPHYSICS

This division supports research aimed at understanding cellular components and how they interact to maintain the function of the cell and the organism. Specific areas of interest include cell organization, movement, and division, as well as the biochemistry of cell membranes. Studies to determine the detailed structures of biologically important molecules like DNA, RNA, and proteins are also an important part of this division's research program. Elucidating a molecule's structure is a key step in determining how it functions--or malfunctions in certain diseases. In addition, the division supports research concerned with the application of engineering knowledge to biomedical problems and the development of new instruments and methods to facilitate research on such problems. The basic research supported by this division will lead to the development of new ways to improve human health.

Among the areas being studied by grantees of this division are:

Solving the Structures of Clinically Important Proteins: The most abundant protein in the human body is collagen. It is the major component of bone and cartilage, and it is also found in skin, tendons, blood vessels, and eyes. Defects in collagen structure occur in certain hereditary disorders, including osteogenesis imperfecta, which is characterized by brittle and easily fractured bones, and Ehlers-Danlos syndrome IV, in which blood vessels rupture and aortic aneurysms can lead to early death. Changes in collagen structure may also contribute to an age-related loss in flexibility.

Understanding of collagen took a great leap forward when Dr. Helen Berman and her colleagues at Rutgers University determined the detailed, three-dimensional structure of a form of the protein. The form they studied contained a mutation that provides information about the structural basis of certain collagen diseases--information that may point to new ways of diagnosis or treatment. This work is also expected to expand knowledge about normal human architecture and about such processes as wound healing and changes in collagen structure with advancing age.

Another important protein structure that has recently been determined is a critical segment of topoisomerase I from the E. coli bacterium. This protein is responsible for unwinding DNA, which is normally tightly coiled in the cell's nucleus, so that the DNA can be reproduced or so that it can provide the instructions for the synthesis of a protein. Dr. James Wang of Harvard University, who discovered topoisomerase in the 1970's, and Dr. Alfonso Mondragon of Northwestern University determined the structure of the topoisomerase and used this information to propose a mechanism for its action in the cell. Because some antibiotics and anticancer drugs interfere with topoisomerase activity, and because this protein is a prime target for the design of drugs against a wide variety of disease-causing organisms, scientists are very interested in information about topoisomerase structure and function.

Understanding Protein Folding: Scientists are actively studying the cellular components and processes involved in the folding of a newly formed, two-dimensional chain of amino acids into an active, three-dimensional protein. Several years ago, NIGMS grantees discovered a class of proteins called chaperonins that promote the proper folding of new proteins and protect them from aggregating with other proteins. Recently, Dr. Paul Sigler and his colleagues at Yale University determined the high-resolution structure of one such chaperonin, named GroEL. The structure, which resembles a doughnut with a large cavity in the middle, indicates that the newly formed protein chain is shielded within the cavity while it folds into its final form. This work, combined with further studies on the mechanism of chaperonin action, will shed light on disorders, such as cystic fibrosis, in which proteins do not fold correctly. It will also help scientists learn how to get synthetic proteins or proteins made through recombinant DNA techniques to fold properly, and will thus be of great benefit to the biotechnology and pharmaceutical industries.

Dr. George Rose of Washington University is approaching the study of protein folding from a different perspective. He is examining the sequence of amino acids in proteins to search for codes that determine elements of folded structure. He has already found sequences that indicate the beginning and end of helical structures within proteins. Further research along these lines should help scientists predict the three-dimensional structure of a protein from its amino acid sequence, and could also enable them to design entirely new proteins for medical and industrial uses.

Deciphering RNA Structure: The discovery in the early 1980's of RNA that could catalyze reactions in much the same way as enzymes do caused scientists to revise some of the most basic principles of biology and led to a Nobel Prize in 1989 for two NIGMS grantees. Now, another grantee, Dr. David McKay of Stanford University, has become the first to determine the detailed structure of a catalytic RNA, in this case one called the hammerhead ribozyme. This work has enabled him to propose how the RNA functions in cutting viral RNA. Because it can be easily adapted to cut any RNA sequence, the hammerhead ribozyme shows promise for eventual therapeutic use against viral RNA's or other RNA's involved in disease. Knowledge about the ribozyme's structure is an important step in this direction.

Scientists Measure the Movement of a Single Muscle Molecule: Dr. James A. Spudich and his colleagues at the Stanford University School of Medicine have managed to measure the forces and distances involved in the movement of a single myosin molecule. Myosin is a molecular motor protein involved in many types of cellular movement, including muscle contraction, embryo development, and the spread of cancer cells. Another protein, actin, works with myosin to produce muscle contraction, but scientists have long wondered exactly how these proteins function on the molecular level. Many researchers believed that movement was produced by a myosin molecule ratcheting along a filament of actin, with each step propelled by one molecule of cellular energy, called adenosine triphosphate (ATP). But this theory was difficult to prove because conventional microscopy is not nearly powerful enough to observe this type of movement. In fact, many of the details of this theory were beginning to be questioned in recent years.

The Stanford researchers used an "optical trap," which consists of tightly focused laser beams that can "grasp" very small objects, to hold an actin filament by tiny plastic beads attached to its ends. The actin was then brought in contact with a myosin molecule that moved the filament, enabling the scientists to measure both the distances moved and the forces exerted. The distance the filament moved was consistent with the one myosin, one actin, one ATP molecule theory.

These studies are not only fundamental to understanding many critical cellular processes that involve movement, they are also relevant to at least one specific disease, called familial hypertrophic cardiomyopathy, in which the myosin molecule is defective.

DIVISION OF MINORITY OPPORTUNITIES IN RESEARCH

The Division of Minority Opportunities in Research (MORE) is the focal point of the Institute's efforts to increase the number and capabilities of underrepresented minority individuals engaged in biomedical research. The goal of the division is to encourage more minority students to pursue training for scientific careers and to enhance the science curricula and research capabilities of faculty at institutions with substantial minority enrollments.

The division has three components: the Minority Access to Research Careers (MARC) Branch, the Minority Biomedical Research Support (MBRS) Branch, and the Special Initiatives Section. MORE's activities give NIGMS the lead role at NIH in research and research training activities targeted to underrepresented minorities.

Minority Biomedical Research Support Branch: MBRS is the largest minority program at NIH. MBRS awards grants to minority institutions to support research projects by faculty members and to provide opportunities for students to work as part of a research team. This support has the added benefit of strengthening the institutions' biomedical research capabilities. Awards are also made to permit enrichment activities, such as attendance by faculty and students at scientific meetings and participation in research during the summer at off-campus laboratories. In FY 1994, 689 faculty members at 99 institutions worked on 593 MBRS research projects, and 914 undergraduate and 422 graduate students participated in these projects as research assistants.

The positive impact of the MBRS Branch is illustrated by the success of these participants:

- Three MBRS investigators have recently received top honors for work in their fields. Dr. Frank Talamantes, a professor of biology at the University of California, Santa Cruz, received the Society for the Study of Reproduction Research Award, a major award given to scientists who study hormones involved in the reproductive process. Dr. George Hillyer, a professor of pathology at the University of Puerto Rico School of Medicine, was elected to the rank of fellow of the American Association for the Advancement of Science. The association elects members in recognition of their distinguished efforts on behalf of the advancement of science or its applications. And Dr. Juliette Bell, a former MBRS participant who is now the MBRS program director at North Carolina's Fayetteville State University, received a Young Investigator

Award from the National Science Foundation. The award offers cooperative research support to approximately 50 of the nation's most outstanding and promising young science and engineering faculty members.

- Dr. Paul Zamora, a former MBRS graduate participant who received a Ph.D. in cell biology from the University of New Mexico, is currently the director of technology and development for Rho Med, Inc., in Albuquerque, NM, and holds a clinical assistant professorship in the College of Pharmacy at the University of New Mexico.

- Dr. Roy McClean, a former MBRS graduate student at New Mexico State University, Las Cruces, recently accepted a tenure-track faculty position in the department of chemistry at the U.S. Naval Academy.

Minority Access to Research Careers Branch: The MARC Branch provides special research training opportunities for students and faculty at institutions with substantial minority enrollments. MARC enables grantee institutions to develop and strengthen their biomedical research training capabilities through improved science curricula, seminars, and off-campus research experiences. As a result, these schools are able to graduate more students who go on to doctoral study and pursue biomedical research careers.

MARC accomplishes these goals through four support mechanisms: honors undergraduate research training grants, predoctoral fellowships, faculty fellowships, and a visiting scientist program. As part of the honors undergraduate program, students are required to have at least one summer research experience at an institution other than their own. A number of these students do their summer research at NIH. In addition, MARC provides conference support to organizations and institutions that are active in the recruitment and retention of minority scientists. In FY 1994, 564 students at 62 institutions participated in MARC's honors undergraduate program, 8 faculty members received training and/or degrees through the faculty fellowship program, and 71 students received MARC predoctoral fellowships.

The following accomplishments attest to the success of the branch:

- Maurice Sholas, a former MARC honors undergraduate student at Southern University in Baton Rouge, LA, and a fourth-year M.D.-Ph.D. candidate at Harvard Medical School, is finishing his dissertation research at the National Institute of Dental Research as a MARC predoctoral fellow. As a MARC honors undergraduate, Mr. Sholas also spent two summers at NIH doing research.

- Serge Jean, a former MARC honors undergraduate student at the City College of the City University of New York, is currently doing research in the department of biological chemistry and molecular pharmacology at Harvard Medical School while pursuing a combined M.D.-Ph.D. degree.

Special Initiatives: MORE also supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. Individuals supported through these special initiatives range from high school students to faculty members. One such initiative is the Bridges to the Future program. This program, which is administered by NIGMS in cooperation with the NIH Office of Research on

Minority Health, encourages students in associate degree or master's degree programs to make the transition to the next level of training (the bachelor's or Ph.D. degree) toward careers in biomedical research. Now in its third year, the program has funded 92 awards, 52 of which were made in FY 1994.

The division recently announced another initiative, the MORE Faculty Development Award. The award enables faculty members to update or enhance their research skills by spending a summer (or one academic term) every year for 2 to 5 years in full-time research in a research-intensive laboratory outside their home institutions. Awardees may also enroll in one academic course per term in fields directly related to their research.

Lastly, the division supports a program of national predoctoral fellowships for minorities. In FY 1994, the fourth year of this effort, NIGMS awarded 49 fellowships, bringing the four-year total to 163.

INTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1994 Actual		FY 1995 Estimate		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
18	$1,136,000	16	$1,105,000	14	$1,010,000	-2	-$95,000

Rationale for the Budget Request

The FY 1996 budget estimate for the Intramural Research Program is $1,010,000, a decrease of $95,000 from the FY 1995 estimate. Funding for the Intramural Research Program during the last 5 years has been as follows:

	Amount	FTE
FY 1991	$1,082,000	18
FY 1992	1,136,000	19
FY 1993	1,180,000	19
FY 1994	1,136,000	18
FY 1995	1,105,000	16

NIGMS has a small, but unique, intramural research program, known as the Pharmacology Research Associate (PRAT) Program. Under its auspices, a group of recently trained scientists is selected each year for a 2-year period of postdoctoral research experience under the direction of preceptors in NIH intramural laboratories. The goal of this program is to develop topflight leaders in pharmacological research who will take key positions in academic, industrial, and government research laboratories.

Profile of PRAT Program Participants: Since its establishment in 1965, 279 scientists have graduated from the PRAT Program. It is known that at least 255 (91 percent) of them have entered research careers. Among these, 119 are located at academic or independent research institutions, 108 are at NIH or other Federal research facilities, and 39 are at pharmaceutical firms. Almost 40 percent of the PRAT graduates who are engaged in research possess an M.D. degree, indicating that the program has succeeded in attracting a large number of physicians and directing them into research careers instead of into clinical practice. This year, a former PRAT fellow, Dr. Alfred Gilman, shared the Nobel Prize in physiology or medicine for his work on the identification of G proteins.

PRAT Fellow Develops Synthetic Peptides that Block Inflammatory Reaction: Dr. Keith Hines, who worked as a PRAT fellow in the National Institute of Dental Research Laboratory of Immunology, used specially designed short lengths of amino acids, called peptides, to block an inflammatory reaction in genetically engineered mice. The mice used in this study were unable to produce a growth factor that regulates the responses of white blood cells to infection or injury, which, in turn, leads to a spontaneous uncontrolled inflammatory reaction.

Dr. Hines hypothesizes that his synthetic peptides work by halting the attachment of white blood cells to blood vessel walls. The long-range aim of research in this area is to be able to treat a variety of debilitating inflammatory diseases such as arthritis and periodontal disease.

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

FY 1994 Actual		FY 1995 Estimate		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
161	$ 25,845,000	166	$26,932,000	165	$27,661,000	-1	+$729,000

Rationale for the Budget Request

The Research Management and Support budget provides funds for salaries, equipment, supplies, and other administrative expenditures that support the NIGMS extramural and administrative staff. The major portion of funds in this budget is reserved for the scientific review and administration of grants and contracts, and for the related fiscal stewardship function. In addition, some funds permit the Office of the Director to direct and oversee the Institute's scientific program activities. Through working relationships with the scientific, academic, and grantee communities, NIGMS continues to be conscious of the public's health and research concerns; these are reflected in the development and planning of the Institute's programs and policies. NIGMS also continues to evaluate its current research portfolio and to determine the need for new or expanded areas of investigation based on promising areas of biomedical research.

The Research Management and Support budget also funds services provided by central NIH components, such as the Division of Research Grants, that are not eligible to receive direct Congressional appropriations; program evaluation studies; and the National Advisory General Medical Sciences Council.

For FY 1996, the Research Management and Support budget request is $27,661,000, an increase of $729,000 above the FY 1995 estimate. Funding for the Research Management and Support budget during the last 5 years is shown below:

	Amount	FTE
FY 1991	$22,626,000	166
FY 1992	24,970,000	173
FY 1993	25,344,000	172
FY 1994	25,845,000	161
FY 1995	26,932,000	166

In FY 1996, NIGMS will continue efforts to streamline its management strategies and develop new administrative processes to enhance its effectiveness and efficiency in support of its mission. Through the use of computer technology, the Institute plans to automate several grants processing procedures and efforts are currently under way to develop a computerized central database of NIGMS grant-related information. In FY 1996, the NIGMS program staff will provide the general oversight and direction for approximately 4,607 grants and 8 research and development contracts to be supported by the Institute. Specifically, the staff's activities include ensuring rigorous scientific and financial administration of grant-supported programs; conducting peer review of competing training grant applications to determine their scientific and program merit; serving as knowledgeable contacts for applicants, grantees, advisory groups, and others; and compiling and reporting scientific and financial information relative to the Institute's grant programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Detail of Full–Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	33	35	36
Office of Administrative Management	36	36	35
Division of Extramural Activities	48	48	47
Genetics and Developmental Biology Division	14	14	14
Pharmacology, Physiology, and Biological Chemistry Division	31	29	27
Cell Biology and Biophysics Division	12	12	12
Minority Opportunities in Research Division	5	8	8
Total, NIGMS	179	182	179

	Average GS/GM Grade
1990	9.8
1991	9.7
1992	10.0
1993	10.2
1994	10.0
1995	9.8
1996	9.8

Note: Includes two FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of Aids Research.

EXHIBIT P

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive level I			
Executive level II			
Executive level III			
Executive level IV			
Executive level V			
Subtotal			
Total - Exec. Lev. Sal			
ES-6			
ES-5			
ES-4	3	3	4
ES-2	1	1	1
ES-1	1	1	2
Subtotal	5	5	7
Total - ES Salary	$512,200	$524,544	$746,106
GS/GM-15	17	16	16
GS/GM-14	21	21	21
GS/GM-13	10	14	14
GS-12	22	27	27
GS-11	5	4	4
GS-10	1	1	2
GS-9	12	13	13
GS-8	7	7	7
GS-7	31	29	29
GS-6	10	16	16
GS-5	9	8	8
GS-4	7	10	10
GS-3	1	3	3
GS-2		1	1
GS-1			
Subtotal	153	170	171

Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	1	1	
Senior Grade			
Full Grade	3	2	1
Senior Assistant Grade	1	1	
Assistant Grade			
Subtotal	5	4	1
Ungraded	11	13	13
Total permanent positions	174	192	192
Total positions, end of year	174	192	192
Total full–time equivalent (FTE) employment, end of year	179	182	179
Average ES level	3	3	3
Average ES salary	$106,106	$107,379	$109,097
Average GS/GM grade	10.0	9.8	9.8
Average GS/GM salary	$31,898	$36,876	$37,466

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office AIDS Research.

TUESDAY, MARCH 21, 1995.

NATIONAL INSTITUTE ON AGING

WITNESSES

DR. RICHARD J. HODES, DIRECTOR
DR. TERRIE WETLE, DEPUTY DIRECTOR
COLLEEN BARROS, EXECUTIVE OFFICER
KARYN S. ROSS, FINANCIAL MANAGER
DR. HAROLD E. VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. We are pleased to welcome this morning Dr. Richard Hodes, the Director of the National Institute on Aging. And if you would introduce the people at the table and then proceed.

INTRODUCTION OF WITNESSES

Dr. HODES. It's a pleasure, Mr. Porter. I'd like to introduce Ms. Colleen Barros, the Executive Officer of the National Institute on Aging, Dr. Terrie Wetle, Deputy Director, and Ms. Karyn Ross, the Director of the Office of Financial Management.

OPENING STATEMENT

Mr. Chairman, I'm pleased to have this opportunity to present an overview of the research programs of the National Institute on Aging. Issues of aging become increasingly important as dramatic demographic changes in the American population move us toward a very different age profile than this Nation has ever before experienced. I'd like to outline for you the magnitude of these particular demographic changes, and then to illustrate the impact of aging research on our understanding of the basic process of aging, and our ability to intervene to prevent disease and to extend independence and high quality of life.

In 1980, there were 23 million Americans aged 65 and over. By the year 2000, this will increase from 23 million to 31 million. And by the year 2040, to more than 70 million Americans 65 and over. These numbers are even more dramatic when one considers the oldest old of Americans, the population 85 and older.

As recently as 1960, there were fewer than 1 million Americans aged 85 and over. By 1980, this had more than doubled to 2 million. By the year 2000, this will double again to 4 million. The prediction is that by the year 2040, there will be more than 18 million Americans aged 85 and over.

The potential impact of this kind of change can be illustrated in the example of Alzheimer's. Alzheimer's disease affects approximately 3 percent of 65-year-olds, but affects nearly half of individuals 85 years of age. The demographic projections that I've outlined for you therefore predict that in the absence of any change in incidence or ability to intervene, there will be an increase of several fold in the prevalence of Alzheimer's disease from the current estimates of 4 million Americans, with an accompanying increase in cost and personal suffering.

The number of research advances over the past year have contributed to the base of information needed to understand the mechanisms underlying Alzheimer's disease, and ultimately to allow effective interventions. Recently, ApoE4, a blood protein that's encoded in chromosome 19, was identified as a major risk factor for Alzheimer's disease. This evening and tomorrow morning you'll be hearing and reading in the press about results of the study that have combined the use of ApoE4 typing together with brain imaging by PET scanning, to identify abnormalities in the brain metabolism in patients who are at high risk for Alzheimer's disease, but in fact who have absolutely no detectable symptoms of the disease, and who by virtue of their age, are not expected to develop symptoms for at least 20 years. This advance opens the opportunity for further investigation into the mechanism of Alzheimer's disease and to interventions which might be initiated at an early stage in the process before there was substantial damage to the brain.

Ongoing efforts are directed to the question of whether ApoE4 protein itself plays a role in susceptibility to Alzheimer's and whether it represents a target for intervention. Other investigators at the same time are studying the potential effects of other genes and gene products. In the past year, there's been success combining the techniques of molecular biology and of transgenic technology to generate a mouse that expresses a mutant beta amyloid protein seen in certain families with Alzheimer's disease. This advance means for the first time some aspects of Alzheimer's disease can be studied by investigators using an animal model.

Over the past year, research in the molecular basis for cellular aging has had a number of notable contributions with impacts across a variety of health issues. NIA grantees identified a protein called P21, which serves as a brake to limit and modify cell replication. In close communication with cancer investigators, it's been demonstrated that P21 plays an important role in mediating the effects of P53, a tumor suppressor gene that has been shown to be mutated in nearly half of human cancers.

These are examples of the importance of long-term funding of basic research that will provide both new targets for directing cancer treatments as well as opportunities for further addressing some of the changes that accompany aging.

In another related area, aging researchers have identified one of the factors that regulates the growth of normal cells by telomere shortening, shortening of structures at the end of chromosomes. In this past year, investigators have shown that human cancer cells express an enzyme called telomerase, which has the unique ability to reverse telomere shortening, and by doing so, may contribute to the ability of cancer cells to grow in an unregulated fashion. Again, this provides an opportunity to both address problems of cancer and some of the other changes that accompany aging.

NIA supports a number of clinical initiatives which address the burdens of physical frailty and of loss of independence, often leading to dependence on long term care. A study reported in the New England Journal of Medicine this past year showed that appropriate exercise interventions were effective both in substantially reducing falls among older people and in increasing strength. It's been shown in these studies that individuals in their 70s, 80s and even 90s, respond to weight training with substantial increases in strength, and moreover, that these increases in strength are translated into improved function in variables such as walking and climbing stairs.

Together with studies that have shown the effect of exercise interventions on cardiovascular status, these findings have created a great deal of public interest as well as interest in the press and by health care providers who provide opportunities for modifying lifestyle in order to decrease susceptibility to serious injury and to illness.

NIA also supports research on social, behavioral and biological factors which affect cognitive changes with aging. Interventions are being devised to improve function in such areas as driving, decision making and the ability to comply with medical instructions. It has been shown that the manner in which information——

Mr. PORTER. Dr. Hodes, I'm going to let these young people come in and sit down. They want a chance to hear you. Please come across.

Sorry for the interruption, but I could see that they are anxious to hear what's going on.

Dr. HODES. Research has confirmed that by designing presentation of information to older people, the ability to comprehend and respond can be dramatically improved, and that appropriate training interventions can reverse and modify deficits in cognitive ability that occur with age.

Overall, advances in behavioral and biomedical research have contributed to our efforts at extending independence and quality of life. Mr. Chairman, the fiscal year 1996 budget request for the National Institute on Aging is $445,823,000. I would be happy to answer any questions.

[The prepared statement and biography of Dr. Richard Hodes follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Aging

Mr. Chairman, I am pleased to have this opportunity to present an overview of the research programs supported by the National Institute on Aging (NIA). Research in aging over the last two decades has contributed to the realization that aging should not be equated with inevitable decline and disease. Consider Alzheimer's disease (AD): This form of dementia has now been linked to alterations in specific proteins and has been shown to affect specific regions of the brain. As a result, it is no longer appropriate to think of "Senile dementia" as the loss of one's memory and mental capacity resulting from the simple process of aging, but rather to understand AD as a disease which should be attacked head-on by the research community. The progress of research on AD provides a model for the successful application of basic research in pursuit of an understanding of disease processes. Basic neurobiology, research on the biology of aging, epidemiology, and molecular genetics have all contributed to an enhanced understanding of AD.

AD will reach critical proportions in the U.S. and other countries as the baby-boom generation ages. Consequently, we face a growing public health crisis unless we can develop interventions to halt or slow the progress of this dreaded disease. Since the prevalence of AD increases dramatically with age after about 65 years, the ability to delay its onset by just five years would substantially reduce the number of cases, and a delay of ten years would largely eliminate AD in the normal human life span. Recently, apolipoprotein E4 (ApoE4), a blood protein whose gene is located on chromosome 19, has been associated with increased risk for AD. This extremely important observation on ApoE4 has been confirmed in a number of laboratories and is the first report of a major biological risk factor of the disease. For the first time epidemiological studies of AD will now have a biological marker for sorting populations into homogenous groups and following them with the hope of finding other risk factors. At the same time, this research has opened the door for new thinking about developing treatment based on the biology of the disease process. The exact role of ApoE4 in AD pathogenesis is still a matter of hypothesis. However, should it be directly involved in susceptibility, this protein would then become an attractive target for interventions. In addition, there are many laboratories currently involved in the identification of other genes associated with increased incidence of AD.

Basic research has applications that cross a wide range of health issues. Where researchers once only theorized about the causes of growing old, they now have the means to track down the actual mechanisms of aging in cells and tissues. Important links are being established between aging research and other areas of biomedical and behavioral investigation. For example, the study of aging at the cellular level now complements research on the mechanisms of cancer. Up to 50 percent of all human cancers are believed to be linked to mutations in the tumor suppressor gene known as p53. The search for the mechanism by which the normal p53 gene controls cell division concluded successfully this year through a confluence of efforts that illustrates the long-term benefits of investment in basic research, the critical relationship between cancer and cellular aging, and an overlooked role that serendipity so often plays in science. NIA grantees, looking for proteins that regulate the cell cycle, targeted their search to the identification of proteins that would bind to an enzyme known as Cdk2 which prepares cells to divide. They found a protein that inhibited this enzyme, which meant that it could act as a "brake" for cell division. As a result of a telephone conversation with an NCI grantee who was working on p53, it was realized that both research groups had isolated the same protein known as p21. This protein, which is elevated in aged cells no longer capable of replication, may contribute to decreased cell division with aging. These new findings will stimulate research on what causes the increased expression of the gene for p21 in aged cells and whether mutations in the new gene lead to cancer, as p53 mutations do. Understanding this aspect of cell cycle control is clinically very important because it identifies specific potential targets for new cancer drugs.

NIA's intramural research initiative on vascular disease has been accelerated because of funds made available in the FY 1995 appropriation. This initiative focuses upon the biology of age-associated changes and pre-disease conditions in blood vessels. Current research is rapidly expanding our understanding of vascular disease, such as atherosclerosis, and provides directions for the development of new interventions. Recent work has shown that the vascular smooth muscle cell, which contributes to the renarrowing of an artery following angioplasty (balloon dilation), is critically dependent on intact "microtubule" function. Intramural scientists have found that the drug taxol, a potent microtubule stabilizing agent, prevents this vascular renarrowing by 70-80 percent in animals. Others are investigating the potential of gene therapy to induce the formation of new blood vessels and enhance blood flow to damaged heart tissues and to prevent artery renarrowing after angioplasty. Advanced glycation endproducts (AGE) are proteins that accumulate in the blood stream and blood vessels of older individuals and interact with specific receptors present on blood vessels. There is a growing excitement about the potential for preventing and/or alleviating vascular disease by targeting these proteins.

Many of our nation's elderly suffer or face death due to diabetes and its complications. A major initiative in NIA's intramural laboratories is underway to develop the basis for new therapeutic approaches to diabetes, including for older patients. Molecular approaches are being used to address the factors responsible for adult late onset diabetes -- an impaired ability of the "beta" cells within the pancreas to respond to blood glucose coupled with a decreased insulin response at target tissues. NIA scientists are pursuing their recent discovery that certain hormones, normally present in the gut, can restore beta cell responsiveness to glucose and increase insulin effects on insulin sensitive tissues. To investigate new approaches to therapy, studies on the treatment of the beta cells with these hormones and their effects on skeletal muscle, a major site of insulin resistance, are being actively pursued.

Even with the hope of major advances in the treatment and prevention of such debilitating diseases, the demand for long-term care is expected to expand in our society. Research will be conducted on many aspects of long- term care, particularly on new and evolving forms of care. NIA supports research on preventing the need for long-term care or institutionalization, enhancing the quality and efficiency of such care, easing the burden of long-term care, and forecasting the requirements for long-term care.

NIA is supporting a number of major clinical initiatives that address the burdensome effects of physical frailty and the loss of independence, which often results in the need for long-term care. Ongoing studies have provided convincing evidence of the benefits of exercise for maintaining independent function in older persons. Two studies have demonstrated the efficacy of specific interventions to improve strength in frail older persons and prevent up to 30 percent of all falls. They have received widespread attention from the public and from health care providers, and have begun to influence health care practices for older persons which could markedly lower the rate of disabling injuries, especially hip fractures.

Osteoporosis is a major contributor towards physical frailty and the loss of independence. Five clinical studies recently funded will determine the contributions of age and ovarian hormone status to changes in bone mass as women approach and cross menopause. Other studies will explore underlying mechanisms whereby menopause-related changes accelerate bone remodelling and adversely impact upon bone mineral metabolism. Future progress in the prevention and treatment of osteoporosis clearly requires an expanded knowledge of the pathophysiology of this disorder. In particular, NIA will seek to support research studies to determine the most appropriate methods for studying the biology of the aging human skeleton. Such an approach will permit us to understand the nature of the age- and menopause-related changes that lead to bone loss. Related to this research direction is NIA's Women's Health and Aging Study which is exploring the causes and course of physical disability, including osteoporosis, in women aged 65 and older.

NIA supports research on social, behavioral, and biological factors affecting cognitive functioning as people age. Efforts are being directed at the implications of decline in cognitive functioning for older people's ability to perform daily tasks, such as driving, decision-making, and understanding and following medical instructions. Of particular importance for such tasks are changes in "attentional resources"-- the ability to identify and process relevant information simultaneously from multiple sources. Research has confirmed that how information is presented to older persons can have a significant impact upon comprehension, and demonstrates the practical implications of basic cognitive research on the daily lives of older people. NIA research has shown that through proper training and practice, certain deficits can be overcome or lessened. NIA has issued a request for grant applications in this area and expects that several awards will be made commencing in FY 1995.

Population aging will become one of the most important social phenomena of the next half century, especially when the now middle-aged baby-boom generation becomes eligible for Social Security and Medicare. How this nation and its institutions accommodate themselves to the dramatic demographic age shift will have a significant effect on the quality of life in the twenty-first century. Research progress in the demography of aging is currently being made in several areas: According to NIA-funded studies, it is evident that the rate of increase in human mortality slows after age 95; possibly even declining after the age of 110, and that centenarians are the fastest growing age group. Such findings are increasingly being used to form actuarial estimates for the Social Security and Medicare Trust Funds. The results of NIA's Health and Retirement Study will be used to study topics such as the influence of health and private pensions on retirement, the impact of changing Social Security's age of eligibility provisions, and the impact of the Americans with Disabilities Act. A related study is following persons aged 70 years and over to examine the interplay of family and economic resources and late life health transitions. To facilitate the use of data from these and other national surveys by the larger research and policy-making communities and in response to Congressional recommendations regarding demographic research, NIA initiated funding for nine Demography Centers.

Dramatic increases are expected in the number of non-minority older people, but the projected growth in the older minority population--over 250 percent by 2030--points to a critical need for additional scientific information. Responding to this need, NIA has increased its funding of minority-relevant research projects from $5 million in FY 1990 to over $30 million in FY 1995. Recent comparisons show that with comparable levels of frailty, African-Americans are less likely to enter nursing homes or enter at older ages than non-minorities. Other findings are that family care is more common than the use of formal care for all minorities, and that recent immigrants are least likely to be institutionalized. Current and future studies, however, are challenged by the need to disentangle the influence of cultural preferences from the effect of socioeconomic differences. Understanding these and other ethnic variations in long-term care has significant implications for the future structuring of formal services and for assisting with the cost-effective alternative of family care.

Mr. Chairman, the FY 1996 budget request for the National Institute on Aging is $445,823,000. I will be happy to answer any questions.

BIOGRAPHICAL SKETCH
Richard J. Hodes, M.D.
Director, National Institute on Aging

DATE AND PLACE OF BIRTH: December 31, 1943; New York, New York

CITIZENSHIP: United States

MARITAL STATUS: Married, one child

EDUCATION:

1965 - B.A., Yale University (summa cum laude), New Haven, Connecticut
1971 - M.D., Harvard Medical School (magna cum laude), Boston, Massachusetts

BRIEF CHRONOLOGY OF EMPLOYMENT:

1968 - 1970 - Research Fellow, Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden
1971 - 1973 - Intern and Resident, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
1973 - 1975 - Clinical Associate, Immunology Branch, National Cancer Institute (NCI), NIH
1975 - 1976 - Investigator, Immunology Branch, NCI, NIH
1976 - 1988 - Senior Investigator and Chief, Immunotherapy Section, Immunology Branch, NCI, NIH
1978 - 1979 - Clinical Fellow, Medical Oncology, NCI, NIH
1980 - 1981 - Acting Chief, Immunology Branch, NCI, NIH
1983 - 1988 - Deputy Chief, Immunology Branch, NCI, NIH
1984 - 1985 - Acting Chief, Immunology Branch, NCI, NIH
1988 - 1993 - Senior Investigator, Experimental Immunology Branch, NCI, NIH
1991 - 1993 - Chief, Immune Regulation Section, Experimental Immunology Branch, NCI, NIH
1993 - - Director, National Institute on Aging, NIH

SOCIETIES:

Diplomate, American Board of Internal Medicine; Board Eligible - Medical Oncology; American Association of Immunologists, 1974 to present; Associate Editor, Journal of Immunology, 1977-1979; Program Coordinator, U.S.-Japan Cooperative Cancer Research Program, 1982 to present; Section Editor, Journal of Immunology, 1985-1989; Chair, Program Committee, American Association of Immunologists, 1986-1988; American Society for Clinical Investigation, 1987 to present; Advisory Editor, The Journal of Experimental Medicine, 1990 to present; Associate Editor, Therapeutic Immunology, 1992 to present; Scientific Advisory Council, Cancer Research Institute, 1992 to present.

HONORS AND OTHER SPECIAL SCIENTIFIC RECOGNITION:

Phi Beta Kappa
Alpha Omega Alpha
Commendation Medal, PHS, 1977
Outstanding Service Medal, PHS, 1988

RESEARCH PRIORITIES

Mr. PORTER. Dr. Hodes, last year you indicated you were in the midst of a planning effort to determine your Institute's areas of greatest scientific need and opportunity. What research areas did you identify as both higher and lower priorities as part of this review, and have you started to plan any new research initiatives as a result of this review?

Dr. HODES. Yes, as I mentioned last year, the Institute has continued to exercise an active planning process in which we look for scientific opportunities of high priority. Some of those areas of high priority were mentioned in my opening remarks. We continue to have strong emphasis and commitment to Alzheimer's disease, in areas of cardiovascular disease, musculoskeletal disease and heart disease.

We have allocated increased funds to a number of areas of high scientific opportunity, including gene therapy which holds promise for future intervention in a number of areas, and signal transduction which as a mechanism underlies the normal and abnormal function of cells in a variety of systems in health and disease, and in the regulation of cell growth and senescence. In addition, there will be a specific initiative in cognitive intervention in which we will apply basic findings from behavioral studies to broader studies to determine the feasibility of improving the cognitive function in some of the practical, day to day variables that I mentioned to you in my opening remarks.

Mr. PORTER. Is it fair to ask you about lower priorities?

Dr. HODES. Yes. You know, of course, at a time when resources are limited, we are making decisions about high priority components within each of those areas I have mentioned. We are responding in large part to the merits of scientific opportunities. One example has been in the area of immunology, where we have had serious questions about the scientific opportunities in the immunobiology of aging. In response to that challenge, with the very strong cooperation of the National Institute of Allergy and Infectious Diseases and Dr. Fauci, last fall we completed a task force meeting in which investigators in aging and in mainstream immunology identified specific opportunities for further research.

In the context of an area which is clearly of importance, but where scientific opportunity needed to be more rigorously addressed, our approach has been to bring in experts that span aging and non-aging disciplines to look for opportunities and to refocus them. That's an example where the priority remains in terms of need, and our search continues for rigorous control of the quality of science.

ALZHEIMER'S DISEASE

Mr. PORTER. Some in the Alzheimer's disease research community are urging as the goal of research the delay of the onset of the disease rather than its treatment and prevention. Is the delay of onset likely to be more easily achieved than either of these other objectives, and what research leads are you pursuing that would delay disease onset?

Dr. HODES. The wisdom behind those remarks is reflected in the demographic parameters that I mentioned for the incidence levels of Alzheimer's disease. Since only 3 percent of 65-year-olds are affected, and incidence goes up to nearly 50 percent by age 85, it's clear that a delay of 5 or 10 years or more in disease onset would substantially reduce the prevalence of disease. Indeed, in almost any biological system, it's easier to intervene in ways that are incomplete rather than those that are complete. There may well be a promise of delay before that for intervention and cure.

In a particular form of Alzheimer's disease, there may be multiple factors contributing to the disease. These factors may relate to oxidative damage that occurs with aging as a part of normal exposure to products of our own normal metabolism. The effects of inflammation and of differences in hormone balance may also contribute to the disease process.

In each of those areas, the research program of the National Institute on Aging and of NIH at large, through cooperation across Institutes, is directed at basic research and at an infrastructure which includes drug discovery programs. These programs take leads, such as the evidence that anti-inflammatory drug history may be protective against Alzheimer's disease, or that use of estrogen therapy in women may be protective against Alzheimer's disease, and translate these leads into the development of drugs to be applied in clinical studies.

In addition to the drug discovery approach, there is a consortium of institutions with Alzheimer's disease patients available for initial experimental studies. In these areas that I've mentioned, studies have begun or will begin later this year in an attempt to define, at least at the level of pilot interventions, whether these is promise in these areas.

Mr. PORTER. Just as a matter of curiosity, has anyone ever looked at the onset of the disease based on the remaining life expectancy of the population to determine whether that's going up or down?

Dr. HODES. There really has not been enough longitudinal study of the disease incidence to answer whether the incidence is changing as life expectancy——

Mr. PORTER. We know it's increasing, but that's because a lot of people live longer.

Dr. HODES. Yes. I think it's really instructive to note the magnitude of advance that has occurred in the field of Alzheimer's disease, such that a few years ago, it was termed senile dementia and hardly appreciated as a specific disease. Only in the past years has it been possible to diagnose with any accuracy the disease. The ability to answer the very important questions you're asking is largely absent.

Some interesting retrospective studies have been attempted which look at such areas as academic performance and writing histories of performance, trying to reconstruct what incidence of disease may have been like some decades ago. But it's highly speculative. Future studies are going to be in a much better position to answer these questions.

Mr. PORTER. This is such a tragic disease, particularly when the onset comes early in life. A woman came in to testify with our public witnesses with her husband. And I think the onset of the disease was in his early 50s, which means that he has a remaining life expectancy of maybe 30 years or longer. And she has to cope with a man who no longer even knows who she is. I can't think of anything more tragic for a family than that.

Dr. HODES. The burdens are staggering. We are all very much impressed with the courage and emotion with which President Reagan announced his own problem. I think this has only heightened public awareness of the issue. There is a subset of Alzheimer's patients with familial forms of the disease that typically have the earlier onset of the form you described. A greater number have later onset.

The notion that 40 to 50 years from now a population of 85-year-olds that might number 18 million may have an incidence of 50 percent or more of Alzheimer's disease is truly staggering in terms of the human as well as cost impact.

Mr. PORTER. It's perhaps fascinating that we have a group of young people here today listening to this testimony who are probably in that exact group that 40 years from now will be in their 60s.

Dr. HODES. Well, they don't look that old. [Laughter.]

Mr. PORTER. Well, maybe late 50s. And it ought to be of great interest to them.

Mr. WICKER. Mr. Chairman?

Mr. PORTER. Mr. Wicker.

Mr. WICKER. I wonder, before you leave the subject of Alzheimer's if I could just follow up.

Mr. PORTER. Absolutely. Please.

Mr. WICKER. When did this condition become known as Alzheimer's disease?

Dr. HODES. It became known as Alzheimer's disease within the last century. A pathologist named Alzheimer so named it. Until that time, it had been called senile dementia, and believed that as people got older, as a normal function of aging, they lost mental capacities. What Alzheimer observed were changes in the brain of patients who had dementia and who had died. The changes were called plaques and tangles, describing the appearance of what was seen pathologically.

For some decades after that description, there was relatively little known about the mechanism of the disease. It was really——

Mr. WICKER. When was his work?

Dr. HODES. Nearly a hundred years ago now.

Mr. WICKER. I see.

Dr. HODES. In the past 10 or 20 years, identification of genes and the gene products which appear to be abnormal and potentially contribute to susceptibility of Alzheimer's disease has really exploded. This is in large measure due to the support of this committee for the National Institute on Aging and all of NIH and its research efforts. The progress to date has been a reflection of basic research which has identified genes and the molecules in the brain that are abnormal. This will provide the essential material for translating this basic information into interventions to slow or block the progression of the disease.

Mr. WICKER. Is it your testimony that the incidence of this disease has not really increased over time, except for the fact that the population is older?

Dr. HODES. I think the simple answer is that we haven't been able to accurately diagnose the disease long enough to answer the question as you put it. The prevalence of disease is clearly increasing because of longer life expectancy. But whether at a given age the incidence of disease is any different now than it was in years past, is essentially impossible to answer. There were many fewer people living to that age years ago, and those who did were not accurately diagnosed.

Mr. WICKER. And how certain are you that this blood protein, ApoE4, is a causation of Alzheimer's disease?

Dr. HODES. It remains to be determined whether the ApoE4 protein is truly a cause. Within the past two years, the first reports occurred of a higher incidence of expression of the ApoE4 protein in individuals who had Alzheimer's disease. ApoE4 and the biochemical and genetic background for its understanding came from studies of those interested in cardiovascular disease. The previously understood primary function of that protein is as a carrier of lipids.

What was shown and confirmed extensively over the past year and a half is that individuals who have one or two copies of an ApoE4 gene, have a higher incidence of Alzheimer's disease than those who do not. That is on strong experimental and epidemiological footing.

The next question to ask, whether the protein itself actually plays a role in disease, is now a process of active investigation, but is not yet conclusive. There are some very exciting findings in a test tube that show that ApoE4, compared to other variations of that protein which differ by just one or two amino acids, have different properties in terms of their ability to bind to amyloid, another protein that's known to be precipitated in the brains of patients with Alzheimer's disease. There's also a difference in ApoE4 and its ability to bind to Tau proteins, which protect some of the microtubular skeleton of nerve cells.

There is thus a plausible scientific basis for understanding a way in which this molecule could play a role, but the actual demonstration that it does play a causal role is as yet incomplete. This is a subject of high interest and priority for support by the Institute.

Mr. WICKER. Thank you, Mr. Chairman.

Mr. PORTER. Let me follow up on those questions. If you had additional funding beyond the request for Alzheimer's, what research topics would you target, and what mechanisms do you use to coordinate Alzheimer's research between your Institute and others at NIH involved in the same subject?

Dr. HODES. Let me begin responding to your latter question and continue on the theme of Alzheimer's disease. Currently, in response in large measure to Congressional request, we are completing a major planning initiative of scientific opportunities in Alzheimer's research. That planning effort is being coordinated through multiple Institutes of the National Institutes of Health, NIA being responsible for approximately 70 percent of the total Alzheimer's related research supported by NIH. The National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health and the National Institute of Nursing Research are among those other Institutes who play an important role, along with other Institutes and divisions.

We have completed a series of three meetings in which major scientists in various fields of prevention, treatment and behavior have come together. Some of the results of these meetings are already published in scientific format. The results of this planning exercise will be presented as a direct report to Congress, and it will reflect coordinated planning efforts across Institutes.

Mr. PORTER. The first part of the question was also related to Alzheimer's, though. If you had additional funding beyond your request, what areas of research would you target in the areas of Alzheimer's disease?

Dr. HODES. The Alzheimer's research area has proceeded so productively as a result of a balance of mechanisms that include a strong reliance on investigator initiated research, as well as a very strong infrastructure that revolves around a centers program. Currently, there are 28 centers, as well as 27 satellite centers that carry the contact and scope of those centers out to areas in the communities. Increased efforts in the Alzheimer's area would again rely on a balance of these mechanisms. The centers provide resources such as patient accrual, pathology, and some of the core laboratory facilities that are required. Investigator initiated research plays a large role in providing individual research topics. The infrastructure allows us to move from basic science to drug discovery to initiating therapies.

I would also point out that, balanced with the very exciting high technology of basic science, is our commitment to care for patients and their families. Behavioral interventions which allow caregivers to better function, including the use of treatments to modify the behavioral problems that accompany Alzheimer's are all high priorities.

Patient education and information and communication to the public and to physicians who are often not completely aware of the research and experimental opportunities in the field, are important parts of the Institute's efforts. This area, along with those previously mentioned, would benefit were there to be greater funds available.

CALORIC RESTRICTION

Mr. PORTER. Now I want to change the subject.

It's been known for some time that caloric restriction extends the life span of rodents. What applications does this have for humans, and do you think that people would be willing to cut their calories enough to extend their life span if that were in fact the case?

Dr. HODES. Mr. Porter, as you mentioned, for decades it's been a very consistent finding in rodents that caloric restriction extends life span. It should be noted importantly that this is caloric restriction, not malnutrition. These animals are very carefully maintained to be sure that they're adequately nourished, but with reduction in calories. The reduction in calories is relative to ad lib feeding of rodents. Rodents are animals that in the wild are out foraging all the time. Reducing their food beyond what they'll eat when given unlimited food in a cage is of significance that is not clearly translated to humans.

There also are two ongoing studies looking at caloric restriction in primate models. The animals are healthy, they receive good nutrition, yet they are calorically restricted. Because the life span of primates is longer than rodents, it will be some time before it is clear whether the same maneuvers that are successful in rodents have application to primates.

I should point out that in many respects, the best hope is perhaps not that we'll find that calorically restricting humans per se will be what benefits health and longevity; but if we can determine what the biologic effects of caloric restriction are, that we may be able to target those in a much more specific and effective way.

In the meantime, it's a challenge to our behavioral scientists to determine how, if it indeed were to be discovered that caloric restriction was of value to humans, that we could obtain compliance with such protocol. We would appreciate your guidance in that area. [Laughter.]

SUCCESS RATES

Mr. PORTER. Since Americans are becoming more obese all the time, even though they know that is a negative health factor.

Yours is one of the few Institutes projecting an increase in its success rate from 1995 to 1996 from 24 to 28 percent. Why do you expect an increase?

Dr. HODES. First, I want to emphasize that these are only estimates. The fluctuation from 24 to 28 percent is within the range of fluctuations seen in past years. I think this primarily reflects the "cycling" of grants. Several years ago, because of an increase to the budget of the Institute, there was a bolus of new grants that when they come up for renewal, causes cyclical fluctuation in success rates. When it recompetes a relatively expensive initiative such as the health and retirement survey, will diminish the number of additional grants that can successfully compete in that given year. So we see this as no substantial trend, beyond the normal yearly cycling.

TELOMERES

Mr. PORTER. A discovery by one of your Institute's grantees was voted by the Harvard Health letter as one of the top 10 medical advances in 1994. The discovery related to the identification of an enzyme that causes ovarian cancer cells to divide indefinitely. The enzyme has since been discovered in a dozen other human cancers. This research project seems to be an unlikely candidate for funding by the Aging Institute. I wonder if you could comment on why you supported it. Does this indicate the serendipity of basic science that we often hear about? You fund a grant with one predicted outcome, and a breakthrough comes in an unexpected area.

Dr. HODES. Wonderfully put. I'd be happy to elaborate on my passing reference to this area which I made in opening remarks.

The initial interest in telomeres by investigators studying aging phenomena, including the distinguished Director of the National Institutes of Health in his own laboratory, was because telomeres appear to influence the very basic functioning of cells, including the stability of chromosomes, the ability of genes to be expressed, and therefore ultimately, the ability of the cells to replicate. Normal human cells, every time they divide, as a reflection of one of the properties of the enzymes which replicate DNA and replicate chromosomes with every cell division, get a little shorter. A little bit is lost from the ends of chromosomes with each division. The ends of chromosomes are what constitute telomeres.

When shortening reaches a critical point, it appears that for normal human cells, cell division stops. This does provide one of a number of checkpoints that prevent uncontrolled growth and replication of cells. This is why this area is of interest to those studying the senescence that comes with aging, that is, what happens to the cell's inherent ability to divide as cells and individuals grow old.

The finding that in cancer cells, telomere shortening with each cell division did not occur, reflected the solution to a puzzle. That is, if cells stop dividing as telomeres get shorter and shorter, how could one ever have a cancer cell? It would appear that cancer cells would need an adaptation to avoid this normal checkpoint. And indeed the enzyme telomerase, as you so accurately describe, is an enzyme which does exactly that. Telomerase is able to add bits of DNA onto the end of chromosomes and reverse the shortening of telomeres that normally occurs.

Because of this ability to bypass this and a number of other normal cellular controls, malignant cells can now grow unchecked. Precisely as you stated, this is an example of serendipity, an educated serendipity, in which investigators in areas of basic science are continuously finding applications unanticipated at the outset of those studies. In this case, the work has shed light on very critical clinical questions of health.

Mr. PORTER. Mr. Wicker?

Mr. WICKER. No, thank you, Mr. Chairman.

HEALTH AND RETIREMENT STUDY

Mr. PORTER. I've been interested for some time in your demography research. Can you tell us what stage of analysis you are in with the health and retirement study, and the oldest old study? How much funding will you have devoted to these surveys by the time they are completed?

Dr. HODES. The health and retirement study has completed its first wave of data collection, which as you are aware, analyzes those events which occur in the transition of life, in this case defined by an age range of 51 to 70, in particular emphasizing the interactions health, economic variables, and decisions to retire.

The related AHEAD survey studies individuals older in age, 71 and beyond, and the way in which material and financial assets determine variables of health. Among the findings we have already derived from these studies are observations that individuals in the work force facing retirement age would rather not have to retire completely, but would prefer to adjust their work schedules. Unfortunately, this is an option which is rarely available in the current employment structure.

The job of data collection for this study has been enormously successful. In fact, the rapid availability of archived data on computer tapes has set a landmark in the field of data collection. What we will be seeing in subsequent years is the utilization of this rich data to carry out further analysis, both through a network of demography research centers and through individual RO1 grants.

The estimated total expenditures in these two programs over a course of a total of 10 years is estimated at $38,000,000.

DEMOGRAPHY RESEARCH CENTERS

Mr. PORTER. There's nine new centers, is that correct?

Dr. HODES. There's a program, yes, of nine new demography centers. I think it's an extremely interesting program that differs from what is conventionally envisioned at NIH as center programs. For the "wet" laboratory sciences or for clinical research, the centers have a very strong physical presence. In other words, the predominant manifestation of these centers are the physical resources.

The demography centers, given that they are staffed by individuals and that computers are real pieces of equipment, constitute an interactive electronic network of demography databases that is going to offer enormous energy to fuel the exchange of ideas, not only just within those nine centers, but within the entire research community. Research impacted by the centers will span topics including economics, cost of illness, interactions of assets and prevention of disease, spanning a wide area of behavioral and biomedical research.

BALTIMORE LONGITUDINAL STUDY OF AGING

Mr. PORTER. You have a unique resource in the Baltimore Longitudinal Study of Aging, which was begun in 1958. What adaptations are you making in the survey to help answer recent research questions?

Dr. HODES. The intramural Baltimore Longitudinal Study of Aging is a unique resource. Having access and the ability to examine individuals periodically over decades has provided some otherwise unavailable opportunities. Perhaps the best publicized and most easily described developed with the discovery of the prostate-specific antigen as an apparent diagnostic risk factor for prostate disease. It became of interest to determine whether the change in prostate-specific antigen level over time, rather than a "snapshot" level was important as a predictor of disease. Because of the existence of our Longitudinal Study of Aging, it was possible to go back to our serum banks and do an immediate retrospective study.

For behavioral studies this is true also. Now that we have developed diagnostic imaging, which can detect some of the manifestations of Alzheimer's disease, we've been able to retrospectively analyze tests of cognition and perception and find those which correlate in a retrospective, but nonetheless a predictive manner, with the onset of Alzheimer's disease.

With so many diseases now becoming amenable to analysis at the genetic and biochemical level, a high priority for the NIA is to capitalize upon the resources of the Longitudinal Study of Aging, by putting together a bank of cellular and DNA material. Should a suggestion of a correlation or relevance of a particular gene or a particular gene product arise, we can examine it not only in a static population, but in a population that has already been studied longitudinally for which we have banked samples.

Among the questions which have arisen lately have been those related to menopause in women. Recruitment has now been modified for a peri-menopausal initiative in which equal numbers of minority and non-minority women are being recruited into the study group. We strive for that kind of flexibility to allow for response to new research questions as they arise.

BEHAVIORAL RESEARCH

Mr. PORTER. The Administration on Aging supports about $25,000,000 of aging research each year. How does your social science and behavioral research in aging relate to their portfolio? Do you co-fund any projects with them?

Dr. HODES. We do co-fund some initiatives and enjoy a very close relationship with Secretary Fernando Torres-Gil and the Administration on Aging. We are co-funding both workshops and investigations that include studies of minority research. I should say that the financial total of the co-funding is modest, but the leverage and expertise offered from combining the two agencies has been quite substantial. Currently, the focus is on planning for the forthcoming White House Conference on Aging. Issues of research, as well as those encompassed by the services supported by the Administration on Aging are integrated very closely.

Mr. PORTER. Can you tell us more about the new study by scientists at NIA that regular exercise such as walking or gardening may cut nearly in half the risk of severe gastrointestinal hemorrhage in older people? I think the study is the first to show an association between physical activity and reduced risk of serious intestinal bleeding.

Dr. HODES. Yes, these studies that were carried out by Jack Guralnik and collaborators at the National Institute on Aging has extended in an unanticipated way, the spectrum of health issues that are affected by exercise. We've become more understanding and receptive to the fact that cardiovascular condition, muscle strength, and so on, are very important to maintenance of general health. But what this study showed was that serious gastrointestinal bleeding was substantially lower in those individuals who showed a history of substantial physical exercise.

Now, this is a correlative epidemiologic study that strongly suggests there might be a causal basis between increased exercise and reduced risk of gastrointestinal bleeding. It must be emphasized that it's only a suggestion at this point. I think where we turn now is to define testable, plausible hypotheses for the ways in which exercise might influence an outcome. The most apparent suggestion is that exercise, because of its influence on overall cardiovascular status, on lipid levels, and on the integrity of circulation through the gastrointestinal tract, decreases the likelihood of gastrointestinal hemorrhage.

But the challenge to uncover the causal basis for the relationship, if there is one, remains at this point. There are some interventions, such as this exercise, which appear to have so many widespread consequences that in addition to looking at specific organ-related issues, a lot of research attention is turned to alterations in basic metabolism involving oxidants and/or anti-oxidant defenses.

This represents yet another challenge to our basic scientists to attempt to understand the nature of such a complex relationship.

LONGEVITY

Mr. PORTER. A final general question, Dr. Hodes. I think we know that genetics play a role in longevity. And we also seem to know that diet, exercise, avoiding toxins like tobacco, a healthy environment, play a role. What do we know about the effects of, or reaction to, perhaps, stress or tension? What do we know about outlook, positive mental outlook? What do we know about the outlook or mental state of individuals, what effect that has on their health and are we studying this kind of thing?

Dr. HODES. I think the short answer is that we don't know enough.

Mr. PORTER. The reason I asked this is that we started this session talking with the Nobel laureates, and someone mentioned Winston Churchill, who smoked big cigars, drank all the time, had a horrible diet, sealed the windows of any place he stayed so the fresh air wouldn't come in, and lived to be 93. That's why the question is one that I think you ought to comment on.

Dr. HODES. Yes, the other example at the Aging Institute we've been fond of is that of George Burns, who was good enough to provide a public service announcement for the Institute. The interviewer asked him the question about whether his doctor frowns upon his smoking of cigars. And George Burns' answer was, "My doctor's dead." [Laughter.]

Seriously, this is an area of active research within the Institute. There are well defined, in both human and experimental models, interactions of environmental and emotional stress between the endocrine and nervous systems. There is no shortage of hypotheses to investigate how some of these externalities can affect physical as well as emotional processes. In all those areas of science, research is continuing. The relative contributions of age, environment and of stress is still not completely understood.

Mr. PORTER. Have we ever studied whether intelligence is a factor in longevity?

Dr. HODES. Level of education, in fact, becomes a very powerful predictor of life expectancy among adults. In some very interesting studies funded by the National Institute on Aging, when one looked at the effects of multiple factors, including ethnic and socioeconomic status as well as level of education, a good part of the difference in life expectancy for adults of different ethnic groups and socioeconomic backgrounds correlated with the number of years of schooling individuals had experienced.

Again this is a very exciting and provocative observation. But as a correlation, it remains to be understood why this is true. That is, are the individuals who receive more education somehow, those who are going to live longer anyhow, or indeed, perhaps the more exciting possibility, is it possible that education itself provides by any or many mechanisms, some advantage in later life. In one of the specific diseases we talked about earlier, Alzheimer's disease, there are strong data to indicate that history of more education, can play a protective role against onset of symptoms of Alzheimer's.

Mr. PORTER. Which may mean that greater intellectual curiosity or challenge throughout one's life, stimulation of the use of your brain, may be a factor in longevity. In other words, a vital interest beyond your immediate surroundings in life.

Dr. HODES. Indeed.

Mr. PORTER. Mr. Stokes?

STROKE

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Hodes, stroke continues to be the third leading cause of death in the United States. And while new research information continues to evolve, this disease continues to take a major death and disability toll on all Americans.

Tell us what major research is underway in this area, and to what extent is there collaboration with the Neurology Institute and also the Heart Institute.

Dr. HODES. The Aging Institute shares very much with Neurology and the Heart Institute this interest in stroke, in particular because it has such a prominent effect on older Americans. There are a number of risk factors for stroke which are areas of very active investigation and priority for the Aging Institute. Hypertension is one of the major risk factors for stroke which has an enormously high prevalence in older people. Hypertension estimates are as high as 60 percent for those aged 65 and older within the overall population, and more than 70 percent for older African-Americans. As many as 80 percent of Black females over age 75, have hypertension.

Hypertension and other aspects of cardiovascular disease are being studied by the Institute on Aging to understand what changes occur during the course of life and whether productive interventions can occur. It has been known for many years that blood pressure tends to increase as people grow older, and this is one of the areas that has been commonly regarded as just one of those things that happen as one ages.

We now know that the determinants of increased blood pressure are many and include a pathology that occurs in the muscle cells within the linings of blood vessels. In studies that have examined the elasticity of normal blood vessels as a function of age, one finds that older people tend to have less elastic vessels. However, when one looks at the variable of exercise and cardiovascular conditioning, one finds that the blood vessels of older Americans who exercise regularly are more comparable in their properties to those of much younger individuals.

We are very actively collaborating this year and in future years with the National Heart, Lung and Blood Institute on initiatives to study effects of intervention on a number of parameters, including those of vascular elasticity. The Aging Institute has recruited a new member for its extramural staff from the National Heart, Lung and Blood Institute to further facilitate our interactions with that Institute in these areas. And within the intramural program, in part thanks to the language incorporated within Congressional Appropriations reports over the past year or two, our laboratory's efforts on vascular and cardiovascular research have also been expanded to meet this scientific challenge.

The Baltimore Longitudinal Study of Aging, which I had discussed briefly some moments ago, has, in recognition of the importance of these vascular issues and that of hypertension, recruited an oversampling from the African-American population. We recognize that this is a population in which the incidence of that disease is increased. The oversampling should provide us the ability to better study the biology and hopefully lead to better interventions to prevent hypertension and other risk factors for stroke.

Mr. STOKES. Doctor, in your Institute, how much is included in your fiscal year 1996 budget for stroke research and outreach?

Dr. HODES. The amount that is designated specifically for stroke research is a little over $7,000,000. This amount does not include related research on cardiovascular disease and neurosciences that are quite germane and important to the overall efforts regarding stroke.

Mr. STOKES. How do these figures compare with the fiscal year 1995 and 1994 funding levels?

Dr. HODES. They show an increase in each of these years that is consistent with the overall increase in the budget of the Institute.

MINORITY HEALTH

Mr. STOKES. In your answer to my first question, you made considerable reference to the minority health problem that we're confronted with. What in your opinion would be the most significant activity underway at your Institute to help address this disparity in minority health?

Dr. HODES. Our overall approach to study a variety of behavioral and biomedical problems has been to include an appreciation of the roles that both ethnic and cultural diversity play for two reasons. The first is that differences in ethnic or genetic variables themselves may help us to understand the nature of the diseases which affect people regardless of minority or majority status.

Second, our responsibility to serve the overall American population requires that we appreciate the differences that occur across our subcomponents. For example, one of the major initiatives of these past years, our extramurally-funded peri-menopausal study involves nine different locations. Among the critical aspects of its planning was an insistence on the ability to compare ethnic groups within each of the centers. So the centers don't all cover the same minority groups, but collectively they sample and oversample groups which differ in ethnic and racial composition to allow us to address whether or not the biomedical, behavioral, and social aspects of menopause differ across ethnic groups.

In the case of the health and retirement study, which was discussed earlier as one of the major demographic studies of the Institute, there was close attention paid to oversampling of minority groups so that differences in health, economic, and retirement behavior parameters could be addressed across ethnic groups.

Within our Alzheimer's research program, the centers infrastructure is comprised of 28 centers. Those 28 centers include 27 satellite centers, all of which draw upon either rural populations, minority populations, or both. We want to include these populations with the ongoing research efforts of the Institute by coupling major academic institutions with these populations.

Mr. STOKES. Doctor, are there significant differences in the prevalence of high blood pressure, stroke and heart failure in men versus women age 65 and over?

Dr. HODES. At age 65 and over, there continues to be an increased incidence in men over women of each of these conditions. But the differences do narrow as one gets to the older survivors, 85 and above. In the case of hypertension, the subgroup identified with the highest incidence, 80 percent, is in Black females, and is even higher than that in Black males.

To put the importance of the minority emphasis within the Aging Institute into a different perspective, although estimates are for a 90 percent increase in the overall population 65 and over by the year 2030, the estimate for the older minority population is a 250 percent increase. The changing demography of our population provides a particular imperative for the Institute to understand and follow the concerns of the elderly, recognizing the growing minority composition of that population.

Mr. STOKES. Is that type of prevalence true in each of these categories, say, for high blood pressure, heart attack and stroke?

Dr. HODES. I don't have available those precise figures for overall cardiovascular disease in African Americans.

Mr. STOKES. You don't have it?

Dr. HODES. I'd be happy to provide that, yes.

Mr. STOKES. Provide that information for the record.

[The information follows:]

According to the National Health and Nutrition Examination Survey (NHANES III), high blood pressure is reported to be present in approximately 71 percent of non-Hispanic blacks age 60 or older. By comparison, NHANES reports that approximately 60 percent of non-Hispanic whites and 61 percent of Mexican-Americans age 60 and over have high blood pressure. It is known that the frequency of high blood pressure in African-Americans is among one of the highest in the world and that, at any decade of life, high blood pressure is more severe in African-Americans than in whites. This higher prevalence for high blood pressure places African-Americans at greater risk for non-fatal and fatal stroke, heart disease deaths and end-stage renal disease. The greater risk for stroke places all African-Americans at a 60 percent higher risk of death and disability than whites. Also, disease of the heart and stroke are the number one and number three leading causes of death in all African-Americans, accounting for approximately 30 percent and 8 percent of all deaths.

INTRAMURAL RESEARCH

Mr. STOKES. In your opening statement, you described research being supported by your intramural vascular disease and diabetes laboratories. Why do you believe this work is so important, and what is the linkage between these two projects and research initiatives that the Heart and the Diabetes Institutes sponsor?

Dr. HODES. In the intramural efforts in cardiovascular disease, I've spoken about it a bit already and have emphasized our interactions with the National Heart, Lung and Blood Institute. Our intramural studies on age-associated changes, including the detection of decreased elasticity in blood vessels, and the consequent changes to cardiac function that were identified in laboratories in the intramural program of NIA have led to efforts in this current fiscal year to establish collaborations with extramural programs of the National Heart, Lung and Blood Institute collaboratively, we will apply this information to studies of broader populations being studied by that Institute.

In the area of diabetes, there has been some very exciting basic science research in the intramural program of the Aging Institute. We have identified a hormone secreted by the gut that influences the responsiveness of cells in the body to insulin. In addition, there has been some basic research that has analyzed the insulin receptor and what modifies or modulates it. These findings are being translated now at a pre-clinical level into studies that may have clinical application.

In terms of clinical studies, the Aging Institute is currently discussing with the Diabetes Institute our participation in a multicenter study for the prevention of diabetes for which we have a strong commitment to focus on older populations, populations that are diverse with age as well as with respect to ethnic groups. We look forward to continuation and expansion of these and other inter-Institute collaborations.

Mr. STOKES. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

This concludes our hearing, Dr. Hodes. Thank you very much. You were excellent in your testimony, and we very much appreciate your appearing before the subcommittee.

The subcommittee stands in recess until 2:00 p.m. this afternoon.

[The following questions were submitted to be answered for the record:]

ALZHEIMER'S DISEASE EDUCATION AND REFERRAL CENTER

Mr. Porter: What is the 1995-1996 cost of the Alzheimer's Disease Education and Referral Center, and how many inquiries did it receive in 1994?

Dr. Hodes: The Alzheimer's Disease Education and Referral Center (ADEAR) is instrumental in distributing Alzheimer's Disease (AD) information to health professionals, patients and their families as well as the general public. In addition, ADEAR develops materials in a variety of media in support of health education campaigns. As a result of America's heightened awareness of AD and related dementias, the ADEAR staff has experienced a tremendous increase in written and telephone inquiries from a conglomeration of audiences. In 1994 alone, ADEAR received 82,022 inquiries, reflecting a 200 percent increase from 1993. The cost of the ADEAR for 1995-1996 is $1,022,000 yearly.

CENTERS

Mr. Porter: Identify the number, type and subject matter of research centers funded in 1995, including the Alzheimer's Disease satellite centers.

Dr. Hodes: In FY 1995, the NIA will support 63 centers. Included are 28 Alzheimer's Disease (AD) Centers, 10 Older Americans' Independence Centers (Pepper Centers), 6 Applied Gerontology Centers, 9 Demographic Centers on Population Aging, 4 Rural Health Centers, 2 Exploratory Centers for Research on Health Promotion in Older Minority Populations, 2 Breast Cancer Centers, 1 Core Center, and 1 Nathan Shock Center of Excellence in Biology of Aging. In addition, the NIA has 27 Alzheimer's disease satellite sites that complement the Alzheimer's Disease Centers.

The Alzheimer's Disease Centers support the full range of Alzheimer's disease research. These centers support shared resources and facilities for research on AD, allowing a number of investigators, many of which are supported directly by the center grants, to provide a multidisciplinary approach to a joint research effort; or, for researchers from the same discipline to focus on a common research problem. The centers also offer ancillary supportive activities such as protracted patient care necessary to the clinical research effort. Additionally, centers serve as regional resources for special research purposes, such as information dissemination targeted towards health practitioners and other outreach activities. The Alzheimer's disease satellite clinics complement the AD Centers by serving as vehicles to target minority, rural or other underserved populations and enhance the clinical research capabilities of the AD centers through the diversification of the research patient pool.

The Older Americans' Independence Centers were authorized by Congress to conduct research on interventions to help older people continue to live independently and avoid institutionalization or prolonged hospitalization. The Applied Gerontology Centers feature studies of social and behavioral interventions to prevent dependence.

The Demographic Centers on Population Aging, initiated in FY 1994, apply state-of-the-art demographic, economic and mathematical methods to new databases and assist in the continuation of demographic research utilizing data gained from studies such as the Health and Retirement Survey. The Rural

Health Centers focus on the changing sociodemographic and epidemiologic characteristics of the older rural population. The Exploratory Centers for Research on Health Promotion in Older Minority Populations, established in FY 1993, study health status, health behavior and practices, and interventions for improving the health of older Black, Hispanic, and Asian Americans.

In FY 1994, the Breast Cancer Centers grants were awarded to develop a broad array of basic, clinical and prevention and control research to reduce the incidence and mortality of breast cancer on a local, regional, and/or national level. The Core Center provides support for the operation of key epidemiological and demographic studies. During FY 1995, the NIA plans to establish the first Nathan Shock Center of Excellence in Biology of Aging. The purpose of this center is to enhance the quality of research in the basic biology of aging, and facilitate the planning and coordination of aging research activities.

ALZHEIMER'S DISEASE

Mr. Porter: How many Alzheimer's drugs are presently in clinical trials and how many are under development in the drug discovery groups?

Dr. Hodes: NIA supports the Alzheimer's Disease Cooperative Study Unit, a 35-site clinical consortium to evaluate compounds for their efficacy in modifying the cognitive decline and the non-cognitive behavioral symptoms associated with Alzheimer's disease (AD).

The first study began in October, 1992 to assess the efficacy of deprenyl and Vitamin E, alone and in combination, in delaying the progression of AD over a two-year period in moderately severe Alzheimer's patients. Enrollment has ended and the last patient will be assessed in November, 1995.

A second drug protocol entitled "Haloperidol, Trazodone, and Behavioral Management Techniques in Alzheimer's Disease Patients with Disrupted Agitated Behaviors: A Controlled Clinical Trial" was developed to target disruptive agitated behavior. Treatment of the behavioral symptoms of AD, such as agitation, is a major problem, especially as the disease progresses, but this issue has not been adequately addressed. This type of trial will help clinicians decide on which class of agent is most effective. This eight month trial began in June, 1994.

The third study, which began in November, 1994, is entitled "A Multicenter Trial of Prednisone in Alzheimer's Disease." Based on evidence that inflammatory and immune mechanisms contribute to neuronal dysfunction in AD, this placebo-controlled parallel design 16-month study will test the hypothesis that broad-spectrum anti-inflammatory therapy with prednisone will suppress deleterious brain inflammation, slowing the progression of the disease.

Finally, based on some preliminary data suggesting a protective effect of estrogen in older women, the next study, scheduled to begin in Fall, 1995, will be a pilot study to assess the effects of estrogen in women who have been diagnosed with AD.

Future consideration will be given to the problematic area of designing trials to evaluate whether a compound can prevent AD. Since AD is a progressive degenerative disease, and it is not clear when the process or processes which result in AD begin, the design of such a trial, the population to use, and the regulatory considerations are issues, among others, which need clarification.

NIA supports six Drug Discovery Groups in Alzheimer's disease. These are preclinical drug discovery and development efforts aimed at facilitating the preclinical development of new compounds for the treatment of AD by expanding the range of approaches to drug treatment. The research efforts of these Groups will identify targets for further drug development. The areas covered include the following: amyloid precursor protein processing and amyloidosis, galanin-acetylcholine interactions, mechanisms of amyloid formation and deposition and neural proteases, second messenger systems, nicotinic cholinergic mechanisms, delivery of peptides to the brain, cell biology of neurotrophins, neurotrophic factor and neurotransmitter delivery to brain by transformed cells, and free radicals and mitochondrial function. Progress is being made in a number of areas and a number of compounds discovered by these Groups will then be further developed so that they can be taken into clinical trials.

A meeting, sponsored by the Fisher Medical Foundation and NIA, was held in May 1994 for the purpose of discussion and development of a long-range plan directed toward accelerating the discovery of treatments for AD. The position papers of the participants, as well as overviews of the discussions, have been published as a special issue of the "Neurobiology of Aging". A number of therapeutic targets were identified as potential treatments for AD and they were ranked both for their rationales and for the time it would take for their development.

Mr. Porter: With former President Reagan's announcement that he is suffering from Alzheimer's disease, interest has increased in the research approaches to the disease. Aside from additional funding, are there particular research mechanisms or approaches that are not presently being used that would advance the progress against Alzheimer's?

Dr. Hodes: Alzheimer's disease research has been hampered by the absence of a systematically collected large data pool. Such data on AD patients would allow epidemiological research related to the identification of risk factors, demographic information important for policy research, and clinical research on disease heterogeneity. At present, the 28 Alzheimer's Disease Centers are collecting information on approximately 30,000 patients and beginning soon, will be collecting data in a more complete and systematic fashion. This data could be stored in a central consolidated database. This would provide an opportunity for study of subgroups of patients from multiple centers. Eventually data could be collected from randomly chosen, population-based subject samples and stored centrally in a large data base in a data coordinating center. With the existence of these new data resources, important new research questions can be posed and answers obtained.

Add-on studies of dementia assessment could be linked to ongoing treatment or epidemiological studies supported by NIA or other Institutes to identify risk factors as well as agents in therapeutic use for other indications and diseases. This approach takes advantage of existing resources because many of these studies are being done in older populations. Better biostatistical methods need to be developed to analyze results from these types of studies. There is also a need to develop simple outcome and follow-up measures that can be easily ascertained for these add-on trials to minimize drop-outs.

New animal models of AD are needed. Because AD currently has the status of a uniquely human disease, it is presently not possible to conduct selected biochemical, molecular, protein, and structural studies that would be possible if this disease could be accurately modeled in animals or in cultured cells. Progress in developing an understanding and effective treatment of AD would be considerably accelerated by the rapid development of in vitro and animal models of AD that display the central features of the disease such as neurofibrillary tangles, neuritic plaques, synapse loss, neuron death, cognitive decline, and spread through the brain in a pattern that mimics that seen in human patients. Recently, a transgenic mouse was developed which expresses a human mutant amyloid precursor protein (APP) gene. When the animals are allowed to mature, they demonstrate amyloid plaque pathology which resembles that seen in human AD. Other aspects of the disease need to be modeled as well, such as neurofibrillary tangles, synapse loss and selective cell death. Animals displaying various features of AD pathology would be very valuable to test potential therapeutic interventions for their impact on these pathological hallmarks of the disease.

New areas of research could be emphasized to enhance scientific progress. Important to the basic understanding of both normal and abnormal functioning in the aging brain are the role of complex proteins. The structure of proteins is obviously dependent upon its primary sequence of amino acid residues. In addition to the sequence of amino acids, a protein's function may depend as much or more on its tertiary or quaternary structure. The transport of molecules and signal transduction, for instance, are often a function of one or more integral membrane proteins. Often these proteins function in association with other membrane-spanning or membrane-associated proteins. Relatively few such proteins are understood in much detail. If continued advances in biology and chemistry are to be made, the detailed structures of additional brain proteins will be required. Some effort to support NMR spectroscopy and x-ray crystallography methods to study these inherently unstable proteins must be developed.

The neurodegenerative diseases of the central nervous system share some common pathologic features, the foremost of which is a gradual, premature, and selective loss of neurons. Neuronal cell death can be viewed as a two-step process. The first step involves some signaling event by typical ligand-receptor interactions and in the second event, "the decision" to commit to a pathway that culminates in the death of the cell. The precise nature or identity of those receptors, ligands and possibly other factors are not known. The physiologic role of cell death, its regulation by lymphokines, cyclins, and kinases, the biological responses (second and third messengers) within neurons, the involvement of the glia, and possible interventions all require further study.

CARDIOVASCULAR RESEARCH

Mr. Porter: As you know, the Committee has expressed an interest in cardiovascular aging research. Can you describe for us how you are responding through your extramural research portfolio, as well as your intramural work in Baltimore?

Dr. Hodes: Although age is perhaps the most potent risk factor for high blood pressure, coronary heart disease, stroke, and heart failure, the precise reasons for this observation are largely unknown. A major mission of the NIA is to elucidate the mechanisms by which the aging process contributes to the development of cardiovascular disease. Ongoing biomedical research supported by the NIA, through both the Institute's extramural and intramural research programs, is currently defining aging changes in the heart and blood vessels and the interactions between these important aging changes and the development of cardiovascular disease. These ongoing studies, added together with important future research opportunities, will contribute fundamental information that may suggest new approaches to prevention and improved treatment of cardiovascular disorders which affect such a high proportion of older Americans.

Through its extramural research program, NIA supports investigator-initiated research on clinical problems that occur predominantly among older persons or that are associated with increased morbidity and mortality in older persons including, importantly, cardiovascular disease. As you know, cardiovascular diseases are among the most common causes of death among the elderly and percentage of deaths due to cardiovascular disease increases with age throughout the later years of life. Age-related changes to the heart (both heart structure and function), the blood vessels (and blood circulation), blood pressure regulation, and lipid metabolism contribute importantly to morbidity and mortality in the elderly. An improved understanding of the causes, rates of progression, and interactions among these important variables (and other related variables including, for example, lung and kidney function), through continued NIA support of investigator-initiated, clinically-relevant research, may lead to new preventive and improved therapeutic interventions designed to reduce the incidence and prevalence of cardiovascular disease in the elderly. As part of its extramural program, NIA is planning to release a program announcement on "Aging, Vascular Stiffness, and Cardiovascular Function." The aim of this announcement is to foster clinical research that will enhance our understanding of vascular stiffness in aging and in cardiovascular disease.

The ongoing intramural effort on age associated vascular disease will continue to capitalize on recent advances. These include the finding that the injury-transformed vascular smooth muscle cell, which is largely responsible for the vascular blockage in restenosis--renarrowing of an artery following angioplasty or balloon dilation--is critically dependent on intact microtubule function. Intramural scientists have found that taxol, a potent microtubule stabilizing agent, prevents this vascular narrowing by 70-80 percent in an animal model without significant toxicity. Others are investigating the potential utility of gene therapy to induce the formation of new blood vessels and enhance collateral blood flow to compromised or damaged heart tissues and to prevent restenosis after coronary artery angioplasty. "Advanced glycation endproducts" (AGE) are proteins that accumulate in the blood stream and blood vessels of diabetic patients and older individuals; these products interact with specific receptors present on circulating blood and blood vessel cells. Intramural scientists, in concert with extramural colleagues, have made a number of recent discoveries that have fueled a growing excitement about the potential role of this system as a novel therapeutic target for preventing and alleviating vascular disease. These include observations suggesting that the signalling pathway activated by this receptor plays an important role in the progression of all vascular disease and that activation of these receptors leads to increased intracellular oxidant stress.

NIA RESEARCH

Mr. Dickey: How do you assure that research done at the NIA is not duplicated at other institutes of the NIH?

Dr. Hodes: Because of the recognition of the need to create a focus for research on aging and the conditions that commonly afflict older Americans, the NIA was established through the Research on Aging Act of 1974. The dramatic projected increase in the older population continues to drive a rapidly growing interest in aging research.

The NIA pursues a basic research program to develop an understanding of aging processes at the biochemical, cellular, and individual levels, and the relationship of these processes to disease and disability. The existence of the NIA as a separate research institute ensures that an integrated approach can be followed to unravel the mysteries of aging and the problems commonly associated with growing older. There is no doubt that because of this focus, research on the effects of menopause, vascular disease, and particularly Alzheimer's disease, just to name several, has advanced much more rapidly than they would have without an NIA.

NIA staff work closely with other NIH components to ensure that our respective research efforts complement, rather than duplicate, each others. Beyond formal means for exchange of information at NIH such as scientific conferences and coordinating committees, many informal networks between NIH scientists help ensure a unified effort in working toward the common goals of eradicating disease and promoting health and independence.

ALZHEIMER'S DISEASE

Mr. Dickey: What recent advancements have been made with regard to Alzheimer's disease?

Dr. Hodes: The discovery of the apolipoprotein E (ApoE) gene on chromosome 19 has proven to be one of the most significant findings in recent years because it has proven to be a susceptibility gene which plays a key role in determining the age of onset of the disease. The ApoE gene as a major risk factor for Alzheimer's disease has been confirmed by over thirty laboratories around the world. Epidemiological studies have indicated that the age of onset can vary by as much as 20 years, depending which form of the ApoE gene a person has. This discovery indicates that the proposed plan to delay the onset of the disease by five, ten or fifteen years is a realistic goal and possible to achieve on biological grounds.

A major theme in Alzheimer's disease is to extend knowledge about the age specific incidence, prevalence rates, and risk factors. The search for risk factors in minority and other distinct population groups could lead to better understanding of the pathophysiology of Alzheimer's disease and contribute to the development of new treatment approaches. These ideas have been the underlying themes for three sets of studies completed over the past year. One group of researchers conducted an incidence study of dementia in relation to education and occupation and found that the risk was greatest for individuals with both low education and low lifetime occupational attainment. A study by another group, done in pairs of older twins, has indicated an apparent inverse relationship of Alzheimer's disease with sustained exposure to steroidal and, possibly, non-steroidal anti-inflammatory drugs, suggesting that these agents may prevent or delay the symptoms of Alzheimer's disease. A third study found that the risk of developing Alzheimer's disease decreased significantly with increasing dose and duration of estrogen replacement therapy, suggesting that estrogen deficiency may be one of the factors that elevates a woman's risk of developing the disease. Estrogen replacement therapy may be useful for both symptomatic treatment and preventing or delaying the onset of dementia in susceptible postmenopausal women. After further preliminary research, clinical trials of anti-inflammatory drugs and estrogen may be initiated.

The clinical diagnosis of Alzheimer's disease has improved as the result of work of many investigators. In specialized research facilities, clinical diagnosis by research neurologists and psychiatrists now approaches 90 percent concordance with the subsequent neuropathological diagnosis. A recent research study has indicated that the combination of genetic analysis and brain imaging using positron emission tomography (PET) can detect brain changes before overt symptoms of AD develop. This kind of information on the accurate early diagnosis of AD will become especially critical as new treatments are developed so that the treatments can be given early in the course of the disease when they can slow or delay the progression of the illness.

AGING ISSUES

Mr. Dickey: With the increase in America's older population, how is NIA prepared to deal with aging issues during the next decade?

Dr. Hodes: Effective planning for the coming demographic revolution becomes essential, and NIA is supporting research to improve forecasting the size, functional status, and ethnic/racial diversity of the older population. Considerable uncertainty exists about the future trends of life expectancy, a variable that has an enormous impact on the Medicare and Social Security Programs. NIA supports research on life expectancy as well as life expectancy free of disability and disabled life expectancy. Research is also supported on other critical components of the variables underlying the impact of the gerontological revolution, including the determinants of retirement, and the determinants of the use of long-term care.

NIA is funding research on accommodations and interventions that can substantially moderate the impact of increasing numbers of older persons. Modifiable factors include altering the age at which people retire, postponing the onset of disability that results in long-term care usage, and reducing the usage of expensive long-term care. NIA sponsored the National Long Term Care Survey that recently found that the prevalence and incidence of disability had declined within the older population between 1982-1989. Understanding how to accelerate this decline could yield great dividends. Several clinical research projects have demonstrated that simple interventions such as very moderate exercise can result in significant functional improvements. If the onset of osteoporosis or Alzheimer's disease could be delayed for five or ten years, their impact could be greatly reduced.

Helping older people with disabilities cope more effectively and improving the system of health care and social services can also have a significant impact. The design and evaluation of health care and social services for an aging population is a major research question that NIA is addressing. NIA currently supports research on who provides what type of care for whom at what benefit and cost. While studies consistently show that families provide the majority of care for older frail relatives, often at great personal cost, new research is suggesting the importance of coordinating home-health services with family and more formal care services as well as the need for integration of acute and long term care.

There is a special need to understand how health-care services are evolving and the consequences of changing health-care structures (e.g., the rapid growth of assisted living facilities) for reducing family burdens and societal costs. NIA is currently embarking on a new initiative to examine aging and health care in a changing health-care environment. This should lead to new research directions on topics such as the influence of changing health care structures and delivery systems (e.g., managed care) on consumer choice, clinical decision making, quality of care, and health outcomes.

Mr. Dickey: What role has NIA played in not only increasing the human life span, but also improving the quality of life for older Americans?

Dr. Hodes: During the last century life expectancy at birth (the average age to which someone can expect to survive) increased substantially. The last several decades have seen an unprecedented and continuing increase in life expectancy at older ages. On the other hand, it is not clear whether or not the human life span, defined as the maximum age to which a human can live (currently about 120) has changed. There are many likely causes for the increases we are seeing in life expectancy, including improved public health, a more educated population, improved health in early childhood, new and more available medical technologies, etc. It is difficult to apportion the influence of any single one of these factors on the increased life expectancy, including medical research.

However, it is probably more important to consider the trend in healthy or disability-free life expectancy which is a good index of quality of life. Until recently, it was feared that as life expectancy increased, a higher fraction of the added years would be spent with severe levels of disability or in institutions. Recent findings suggest that the opposite might be true: disability rates might be decreasing. Most of NIA's research program is devoted to the aim of decreasing disability, and more generally, thus increasing the quality of life of older people. While health is probably the most important factor in quality of life, many other factors are also important including family, financial condition, and what might be considered successful psychological aging.

Through its extramural and intramural research programs, the NIA is providing fundamental scientific knowledge about the processes of aging and the problems and concerns affecting people as they age and in their old age. This information forms the basis for clinical practice as well as for social and behavioral interventions for improving (active) life expectancy and the quality of life for older Americans.

Recent research efforts are focusing on designing and evaluating interventions that can make a difference in older people's everyday lives. One major effort, the Roybal Centers for Applied Gerontological Research, is investigating strategies for designing scientifically rigorous programs that can foster the continued driving performance of older persons, enhance the physical functioning of home-bound elderly, create more positive caregiving behaviors in nursing-home settings, and increase productive work roles and volunteering in the later years of adulthood.

Other examples, which are disease specific, involve research on restructuring the living environment, changing the ways in which care is delivered, or improving older people's ability to cope with chronic illnesses and disability. For example, NIA is supporting an ongoing collaborative effort to evaluate the effectiveness of special dementia care units for improving the quality of life of cognitively impaired nursing home residents and reducing the burdens of care. These studies will be complemented by a new initiative to test different strategies for enhancing family caregiving for persons with dementia (e.g., use of social support groups, respite care or new technologies to reduce the burdens of care).

Prevention is a major concern at NIA, and we are currently supporting research on self-care behaviors that can help older people maintain their health and functioning. We are supporting several research studies that examine how older people evaluate their health and make choices about their health care. NIA is also funding a variety of research studies on the best strategies for encouraging older people to become more physically active, examining both facilitator and barriers to sustained behavioral change. Moreover, NIA is encouraging studies directed at improving doctor-patient interactions so that older patients better understand their health conditions, identify early illness symptoms correctly, and follow recommended medical advice, all of which can impact on an older person's health and quality of life.

Physical frailty and mobility impairments can also have profound effects on the quality of life of the elderly. For example, the likelihood of nursing home admission more than doubles when an elderly individual is unable to perform one or more activities of daily living. Moreover, approximately 16 percent of community-dwelling elderly (aged 75 and older) experience deficits in activities of daily living each year. One of the approaches being used to improve the quality of life of the elderly is the development of interventions to improve physical performance abilities, both in physical measures such as strength and balance and in the prevention of falls. Analysis of results from a recent clinical trial on frailty and injuries indicates that: 1) "targeted intervention" strategy with a variety of risk factors for falls (e.g., sedative use, multiple medication use) can be effective in reducing falls; and 2) balance, strength and endurance training can markedly improve physical performance in community-dwelling and very frail nursing home residents.

ALZHEIMER'S DISEASE

Mr. Stokes: According to your opening statement, a head-on attack by the research community is required to effectively address Alzheimer's disease. What is the extent of this health problem in the United States? What would be the impact if we could delay the onset of the disease by five to ten years?

Dr. Hodes: As a greater proportion of the population survives beyond the age of 85 years, increasing numbers of individuals will be at risk for developing a dementing disorder such as Alzheimer's disease (AD). It is estimated that by the year 2050 there will be over 14 million individuals affected by some form of dementia requiring care and institutionalization.

The challenge of reducing the numbers of individuals with AD is made particularly difficult by the demographic trends in the age distribution of the U.S. population. For example, the U.S. Bureau of Census data indicate that between 1980-1990, the 65 and over age group increased at a substantially higher rate than any other age group. The prevalence of AD more than doubles every decade past the age of 65. For example, the prevalence rate for the 65-74 age group is about 4 percent and increases to 16 percent for the 75-84 age group and it goes up to a 47 percent prevalence rate for the 85+ age group. Although somewhat different prevalence rates are reported by different studies, almost all of them find an exponential increase in prevalence rates as a function of increasing age. Such studies have well established that aging is a strong risk factor. The strategy of delaying the onset of disabling symptoms by five years for all age groups beyond 65 will reduce nearly by half the total number of individuals affected by the disease.

The rising cost of long-term care in recent years has made the economics of health care one of the most important issues in the array of major public health concerns. AD, with its long clinical course, is one of the most significant disabilities requiring various forms of long-term care services in different settings ranging from home care to nursing homes. The burden of care to the families of AD patients is not just emotional stress and physical hardship, but financial cost as well. It is estimated that the total annual direct and indirect cost of care for AD to the country as a whole is between $90 - 100 billion. The cost of disability most immediately affects the families of AD patients, but ultimately has major economic impact on society at large by reducing or impairing potential productivity. The long clinical course of the disease, its devastating effects on the ability of the patient to function independently, the psycho-social stress on the families, and the heavy economic burden associated with care, have combined to raise public awareness and concern about the lack of any means to cope with this. The discovery of safe and effective treatments is an urgent public health challenge. The potential significance of an effective treatment which would slow or reverse the disease or ameliorate the cognitive or behavioral symptoms would be enormous from a variety of perspectives including the increase in intellectual, emotional, and social well-being of the affected individual and his/her family and the caregivers and the decreased economic costs to families and society.

Mr. Stokes: With respect to progress, what can you tell us this year that you could not tell us last year?

Dr. Hodes: The discovery of the apolipoprotein E (ApoE) gene on chromosome 19 has proven to be one of the most significant findings in recent years because it has proven to be a susceptibility gene which plays a key role in determining the age of onset of the disease. The ApoE gene as a major risk factor for AD has been confirmed by over thirty laboratories around the world. Epidemiological studies have indicated that the age of onset can vary by as much as 20 years, depending which form of the ApoE gene a person has. This discovery indicates that the proposed goal of delaying the onset of the disease by five, ten or fifteen years is possible on biological grounds. Other important findings which fuel the optimism of the scientific community include the results of epidemiological studies which indicate that education might be protective against the onset of symptoms.

Mr. Stokes: As we learn more about the mechanisms underlying Alzheimer's disease, how is that knowledge being applied to further advances in the development of prevention and treatment interventions?

Dr. Hodes: A recent research study has indicated that the combination of genetic analysis and brain imaging using positron emission tomography (PET) can detect brain changes before overt symptoms of AD develop. This kind of information on the accurate early diagnosis of AD will become especially critical as new treatments are developed so that the treatments can be given early in the course of the disease when they can slow or delay the progression of the illness. Until the late 1980's, the prospect of developing effective treatments for AD was very remote. However, during the last few years the prospects of discovering useful compounds have improved significantly. In a very short period it was discovered that the clinical symptoms of AD, such as cognitive loss, are associated with a specific biochemical deficit in the brain. This finding eventually led to the testing and approval of the first drug treatment for AD. Now many other second generation compounds are in various stages of development and testing; these are expected to provide safer and more effective drugs. Since 1978 remarkable progress has been made in understanding the molecular details of the hallmark neuropathological lesions associated with AD such as the protein chemistry of the amyloid in the senile plaque, the abnormal process of adding phosphate molecules to the tau protein in the tangles, and the mechanisms of losing contact points between nerve cells (synapses). These findings have led many biotech companies to begin formulating strategies to slow down or reverse the destructive course of these molecular lesions. Meanwhile, studies of the genetic basis of this disease have been incredibly productive in identifying three chromosomes (21, 14, and 19) associated with AD, and the prospect of discovering yet additional genetic loci on other chromosomes is very promising.

Preliminary results of pilot epidemiologic studies have indicated that treatments with some well known products already on the market such as estrogen and anti-inflammatory compounds may also have a positive effect in delaying the symptoms of AD. These findings now are being tested for proof of concept. More recently, the development of a mouse model for one of the brain lesions (the deposition of amyloid proteins) associated with AD will allow scientists to test new drugs and explore ways to prevent the development of these lesions.

Extrapolating the current rate of progress in understanding the neurobiology of this disease into the future, there is sufficient justification for optimism that expansion of ongoing efforts to discover risk factors, cause(s), and treatments will be successful in achieving the goal of delaying the onset of disabling symptoms and maintaining independent functioning.

NEUROLOGICAL RESEARCH/ALZHEIMER'S DISEASE

Mr. Stokes: Last month, the Committee had the opportunity to hear testimony from the nation's Nobel laureates. They indicated that neurological research was one of the most important areas that, if enhanced, offered considerable opportunity to further medical advances. To what extent is this area of research a high priority for your Institute and how is it being used to help unravel and increase our understanding of Alzheimer's disease?

Dr. Hodes: The Neuroscience and Neuropsychology of Aging Program of the NIA supports a broad spectrum of research aimed at a better understanding of age-related normal and pathological changes in the structure and function of the nervous system and how such changes affect behavior. The basic mission is to expand knowledge on the aging nervous system to allow improvement of the quality of life for older individuals. This mission includes basic and clinical studies of the nervous system, clinical trials of interventions of therapeutic modalities, and epidemiologic research to identify risk factors and to establish prevalence and incidence estimates of pathologic conditions. In addition, research is supported that is relevant to those geriatric problems arising from psychiatric and neurologic disorders associated with aging.

The NIA legislative mandate provides specific authority to support research on AD, establish the Alzheimer's Disease Patient Registry program, conduct clinical trials for the treatment of AD, and promote research on the etiology, treatment, and diagnosis of AD. The research program related to AD is of high priority to the Institute. The NIA's commitment to the systematic study of the aging brain began in 1978 with the creation of the neuroscience of aging program. Through its investment in neuroscience research, the NIA is committed to solving not only the problems of dementias of old age, but also to further understanding of the normal aging brain.

Mr. Stokes: How much is included in your FY 1996 budget request for neurological research and for Alzheimer's research? For each, how does the FY 1996 estimate compare with 1995 and 1994?

Dr. Hodes: The FY 1996 NIA budget request contains $220,700,000 for Alzheimer's disease research; the FY 1995 estimate is $216,360,000 and the FY 1994 actual was $212,797,000. The FY 1996 request includes $182,850,000 for neurosciences research with a FY 1995 estimate of $179,250,000 and a FY 1994 actual of $174,027,000.

SPECIAL POPULATIONS

Mr. Stokes: Please describe NIA's efforts to ensure that the particular concerns of minorities and women have not been overlooked in research, research training, and outreach funded by the NIA.

Dr. Hodes: In 1988 the NIA established a staff Working Group on Minority Aging to provide continuing advice on research and training programs focusing on minority health and training of minority investigators. In addition, a subcommittee on minority aging of the National Advisory Council on Aging has been established to provide continuing advice to the Director regarding minority initiatives. These two groups aid in the development and implementation of strategies in minority health and aging and minority training.

A series of regional workshops sponsored by the NIA Working Group on Minority Aging was begun in 1993. Each of the regional workshops focuses on a specific ethnic minority group and provides input on diseases/disorders, and behavioral and social conditions which are important to improving minority health status. The first regional workshop was held in Atlanta, Georgia and focussed on the African American population; the second workshop was held in Los Angeles, California and focussed on the Hispanic population; the third workshop was held in Albuquerque, New Mexico and focussed on the American Indian population; a fourth workshop will be held at the NIA's Gerontological Research Center in Baltimore, Maryland in April 1995. In addition to information on NIA extramural programs, this fourth regional workshop will have the added feature of focusing on the intramural program and opportunities for research training and employment in that program. NIA plans to hold a fifth regional workshop at the Exploratory Center for Research on Health Promotion in Older Minority Populations in Chicago, Illinois in May 1995.

Recently, NIA and the NIH Office of Research on Minority Health sponsored a technical assistance workshop for minority investigators to provide information on the application process. The workshop included the presentation of case studies by experienced investigators demonstrating approaches to research design variables such as sampling and data analysis. In collaboration with the Gerontology Society of America, NIA provided funding and assisted in the development of the Second

Annual Minority Predoctoral Leadership Development Awards. Eleven predoctoral students from a range of scientific disciplines were selected to participate in the yearlong program.

The satellite diagnostic and treatment clinics were established to increase the heterogeneity of the research patient pool and to enhance the research capabilities of the Alzheimer's Disease Centers. The satellite clinics serve as vehicles for the recruitment, diagnosis and management of Alzheimer's disease patients and their families, who are then offered the opportunity to participate in research protocols and clinical drug trials. These clinics are targeted to minority, rural or other underserved populations.

The Exploratory Centers for Research on Health Promotion in Older Minority Populations were initiated to study health status, health behavior and practices, and interventions for improving the health of older Black, Hispanic, and Asian Americans. The NIA, the Administration on Aging, and the Gerontological Society of America recently held a conference on the future of minority aging research. The conference focused on identification of key methodological issues in conducting research on elderly minority populations, as well as development of a clearer definition of the concept of cultural relevance in interpreting research findings. An overview of the proceedings and recommendations is currently being prepared. In October 1994, NIA and the Roybal Institute on Applied Gerontology in Los Angeles held a workshop focusing on the translation of research findings in the area of elderly Hispanic health status into policy recommendations affecting the development of health services. Issues of problem identification, prevention, rehabilitation, and outreach were discussed within the context of the recent research findings uncovered by the NIA-funded research projects. A summary of the workshop recommendations is currently being prepared.

NIA has a strong commitment to address the health problems of particular concern to women as typified by the following recent initiatives:

--A request for applications (RFA) was issued for research on various aspects of menopause as part of a major NIA initiative to discover the natural history of the menopause, its physiological and sociobehavioral antecedents and consequences, and the dynamics of hormone replacement therapy and therapeutic alternatives. These studies will enhance understanding of the role of menopause in chronic diseases such as osteoporosis, cardiovascular disease and urinary incontinence, as well as an understanding of why some women experience symptoms while others do not. Improved knowledge is essential in formulating strategies to prevent these diseases or conditions and to ameliorate symptoms and thus improve the quality of life in middle-aged and older women.

--Enrollment of women in the intramural program's Baltimore Longitudinal Study of Aging (BLSA) has increased to enhance the perimenopausal study. This study will measure hormonal changes in African-American and Caucasian women as they go through menopause and relate these hormonal changes to consequences, such as losses in bone density and strength, changes in body composition, and development of cardiovascular outcomes and metabolic diseases.

--Women participants in the BLSA will also be subjects for the Vascular Initiative, which will examine age, race, and gender differences in blood pressure, arterial stiffness, and cardiac structure and function in African-American and Caucasian participants, with a special emphasis on discovering the cause of the dramatic rise in the incidence of hypertension, heart attacks, and strokes in women after menopause.

--In FY 1994, the Breast Cancer Center grants were awarded to develop a broad array of basic, clinical and prevention and control research to reduce the incidence and mortality of breast cancer on a local, regional, and/or national level.

BREAST AND PROSTATE CANCER

Mr. Stokes: How extensive is breast cancer and prostate cancer in the elderly population? What is the extent of the research that is underway at the institute in each of these areas?

Dr. Hodes: Breast cancer and prostate cancer are very extensive in the elderly population. National estimates compiled by the American Cancer Society (ACS) for 1994 were that 182,000 new cases of female breast cancer would occur, and that 200,000 new cases of prostate cancer were expected. While the ACS did not provide estimates for the older population specifically, it is known from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program, a population-based tumor registry, that 50 percent of all breast cancers occur in women 65 years and older; 84 percent of prostate cancer occurs in men 65 years and older. The highest rates of breast cancer are in women aged 65 years and older reaching over 400.0 per 100,000 population. Peak rates of 483.9 and 477.1 per 100,000 are observed in the 75-79 and 80-84 years age groups. Prostate cancer incidence rates for men aged 65-69 are 661.0 per 100,000, a very high rate in and of itself, but even higher rates, ranging from 1,019.8 to 1,363.3 per 100,000, are observed for men 70 years and older.

The NIA has research underway addressing breast and prostate cancers in both intramural and extramural programs. We have collaborative studies underway with the NCI using six of the SEER tumor registries to investigate cancer in the elderly. The studies include breast and prostate tumors as well as five other malignancies that affect older persons to a great extent. Specifically, we are looking at how concomitant chronic conditions and/or illnesses influence the extent of disease stage at initial diagnosis, first course of therapy, illness behavior of the elderly, and patient perceptions of their need for medical assessment. The focus is on persons 65 years and older.

NIA has also supported breast cancer research in older-aged women under extramural research solicitations. For example, in 1994, the NIA funded two planning grants and several research projects for breast cancer research programs. The NIA is funding one of six cooperative agreements for the "Cooperative Network for Molecular Genetic Markers of Prostate Cancer"; the NCI is funding the other five sites. The network investigators are identifying markers that a) distinguish indolent from aggressive disease, b) characterize the increased incidence of disease in patients of advanced age, and c) define the biological behavior of prostate cancer in black and white patients. Two other NIA-funded studies are examining fundamental questions regarding prostate biology that impact on the development of prostate cancer.

Intramural scientists in the Baltimore Longitudinal Study of Aging are conducting a ten year study of the causes and natural history of prostate cancer, benign prostatic hyperplasia (BPH) and normal prostatic growth in Caucasian and African-American men. Researchers will continue to investigate potential uses of rates of change in prostate-specific antigen (PSA) levels to improve clinical detection of prostate cancer and benign prostatic hyperplasia (BPH). Recent findings suggest that: 1) rates of change of PSA are significantly more accurate than the traditional single measure for the early detection of prostate cancer; 2) certain PSA criteria now in use may lead to many unnecessary prostate biopsies and should be dropped from clinical practice; and 3) PSA tests may be useful in guiding optimal treatment decisions for BPH. The high morbidity, mortality, and economic costs related to prostate cancer make it imperative to improve knowledge regarding its etiology, early detection, and treatment. Interest in early detection has risen because of the increasing use of prostate-specific antigen (PSA) tests in clinical practice. Treatment issues are even more important now because PSA testing has led to a dramatic increase in the number of detected prostatic cancers.

DIABETES

Mr. Stokes: Nearly 14 million Americans have diabetes, and worse, nearly half of them are not even aware that they have the disease. What is the extent of diabetes in the elderly population? African Americans, Hispanics, and other minorities suffer a disproportionately high rate of diabetes as compared with the general population. Additionally, the number of amputations associated with the disease is extremely high, what can you tell us about this problem, and about what is being done to resolve it?

Dr. Hodes: Diabetes, especially non-insulin-dependent diabetes mellitus (NIDDM), is prevalent in the elderly population. In older persons age 55-64, the prevalence of NIDDM, both undiagnosed and diagnosed, is approximately 13.4 percent of the U.S. population. Moreover, between the ages of 65-74, NIDDM prevalence increases to 18.7 percent of the U.S. population.

Important findings from the Diabetes Control and Complications Trial, supported by the National Institute of Diabetes, and Digestive and Kidney Diseases, suggest that daily management of insulin-dependent diabetes mellitus (IDDM), by maintaining one's blood sugar level as close to normal as possible, can help prevent or delay several deleterious complications including damage to the nerves, eyes, and kidney. There is now interest across the NIH to explore the possibility of whether daily blood sugar control in patients with NIDDM will have a similar result. If so, then the vascular disease and potential limb amputation in these patients could be delayed or avoided as well.

Our Baltimore Longitudinal Study of Aging has provided unique information on the rate of development of diabetes in men and women across the entire adult age spectrum. The study has quantified the relative influences not only of age itself but also of the degree of obesity, the relative distribution of fat in the body, and of the fasting blood glucose levels and the results of glucose tolerance testing over a period of thirty years of the adult life span on the risks of developing the disease. The study demonstrates that diabetes incidence increases progressively into very old age and that preventive strategies certainly should be undertaken and might very well be even more successful (in quantitative terms for diabetes prevention) for older than for younger adults.

NIA funds social and behavioral research on the ability of the elderly to recognize and manage chronic illnesses such as diabetes. Studies indicate that if older people conceptualize their problems simply as caused by age, they are less likely to seek medical treatment than if they see their symptoms as illness related. This finding highlights the importance of educating older people and their doctors about common symptoms which might be misinterpreted, often resulting in delays in receiving appropriate medical care.

Effective management of diabetes depends upon adherence to proper diet, regular exercise, appropriate foot care, and compliance with any prescribed insulin therapy. Assuming proper diagnosis, the quality of the doctor-patient relationship is seen as a critical factor in determining older people's follow-though on recommended regimens. Since older people have generally been ignored in studies of doctor-patient relationships, NIA is intensifying research efforts in this area with the goal of improving compliance with recommended treatments. Early diagnosis, changes in health behaviors, and improved care should reduce some of the negative outcomes of diabetes, such as amputations. In the meanwhile, NIA is supporting research on the adjustments of older persons who experience lower limb amputation.

FRAILTY IN THE ELDERLY

Mr. Stokes: Loss of physical independence remains a major concern for the elderly. Many believe that this phase of the aging process can be slowed with reasonable exercise and attention to muscular deterioration, and that as a result there would be a reduction in number of the medications they have to take. What can you tell us about the benefits of reasonable exercise in the elderly? What research is underway and planned to address this ongoing health problem?

Dr. Hodes: Age-related decreases in muscle mass and strength have been shown to significantly contribute to falls, the loss of physical functional independence and may even play a role in the development of chronic diseases (such as diabetes and osteoporosis) in the elderly. Such age-associated changes in skeletal muscle are thought to primarily result from the lifelong accumulation of inactivity, but ongoing studies suggest that endocrine status, metabolism and nutrition may also be important factors. With respect to physical functional capacity, recent studies have demonstrated that moderate strength and weight training programs can improve balance control, walking speed, ability to climb stairs, rising from a chair and flexibility in the elderly. Ongoing research in this area has been directed towards: 1) systematic identification of key muscle groups necessary for different activities of daily living; 2) detailed characterization of aged muscle (in terms of structure and function); and 3) greater understanding of underlying causes of age-related muscular deterioration. These types of data are crucial in designing more effective, "targeted" types of interventions in the future which could prevent the loss of functional independence and/or improve the functional capacity of the aging population.

Mr. Stokes: Also, with the increasing sedentary lifestyle among all ages of the U.S. population even in children, what is the projected extent of this health problem? What is the significance of the relationship between exercise and bone mass and improved health?

Dr. Hodes: Frailty in the elderly is often associated with decreased skeletal muscle mass/strength and the presence of chronic diseases (including osteoporosis), both of which have been substantially attributed to a sedentary lifestyle. It was recently reported that eight out of ten individuals, aged 60 and older, either have one or more chronic diseases or are functionally impaired. By the year 2020, the number of individuals in the age group of 65 and older has been estimated to be 51 million, and by the year 2040 this group will increase to 67 million. Consequently, the health burden associated with physical inactivity will continue to be substantial, and it is likely that a variety of interventions will be needed to deal with this growing problem in the aging population. While exercise is generally recognized to promote good health at all ages, it is important to keep in mind the diversity of the elderly population (e.g., differences in health status, lifestyle, risk factors). Clearly, strategies for health promotion and prevention of diseases need to be implemented both in younger populations to encourage lifelong healthy habits and also in the increasing population of the elderly.

AGING RESEARCH

Mr. Stokes: Please describe the most promising opportunities in basic as well as clinical aging research you see for the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Hodes: As aging becomes a topic of increasing public concern, interest in interventions to delay or eliminate the consequences of aging has grown enormously. Over the past year, basic research in the molecular basis for cellular aging has had a number of notable contributions with impacts across a variety of health issues. For example, oxidative damage for critical cell components is chronic and ubiquitous in living cells. When oxidative stress overwhelms the cellular defense and repair systems, an alternative protective strategy for the organism is for the damaged cell to actually "commit suicide." Whereas this may be the best way to eliminate a heavily damaged and potentially cancerous liver cell, the elimination of a neuron (for example, a brain cell) has more serious consequences because of the inability to replace lost neurons. Thus, an understanding of how cell death is regulated may be crucial not only in preventing cancer, but also in preventing neurodegenerative disease.

Important links are being established between aging research and other areas of biomedical and behavioral investigation. NIA grantees identified a protein called p21, which serves as a brake to limit and modify cell replication. In close communication with cancer investigators, it has been demonstrated that p21 plays an important role in mediating the effects of p53, a tumor suppressor gene that has been shown to be mutated in nearly half of human cancers. Beyond contributing to an understanding of cellular aging, this finding could have important implications regarding the understanding of and eventual treatment for cancer.

Alzheimer's disease (AD) is a high research priority for NIA. It currently affects an estimated four million older Americans and their families, causes enormous personal suffering, and costs the nation billions of dollars each year. NIA devotes over $200 million annually to Alzheimer's disease research. Without the development of new treatments, cures, or preventive approaches to this dreaded disease, the number of individuals and families devastated by AD will likely increase up to five-fold within the next 50 years. Consequently, we face a growing public health crisis unless we can develop interventions to halt or slow the progress of this disease. Recently, apoliprotein E4 (ApoE4), a blood protein whose gene is located on chromosome 19, has been associated with increased risk for AD. This extremely important observation has been confirmed in a number of laboratories and is the first report of a major biological risk factor of the disease. For the first time epidemiological studies of AD will now have a biological marker for sorting populations into homogenous groups and following them with the hope of finding other risk factors. At the same time, this research has opened the door for new thinking about developing treatment based on the biology of the disease process. The exact role of ApoE4 in AD pathogenesis is still a matter of hypothesis. However, should it be directly involved in susceptibility, this protein would then become an attractive target for interventions. In addition, there are many laboratories currently involved in the identification of other genes associated with increased incidence of AD.

Because aging results from both genetic and environmental factors, appropriately designed genetic interventions may be able to slow aging due to both kinds of factors. For example, increased expression of genes for antioxidant enzymes might be effective in reducing damage due to oxidative stress in specific tissues. If specific age-related degenerative changes can be delayed by genetic intervention, high quality of life can be maintained and health care costs can be delayed until later in life. This will be of particular benefit if the period of time ultimately spent in ill health can be shortened, and if the severity of the loss of function can be attenuated, thus reducing overall health costs.

NIA's intramural research initiative on vascular disease has been accelerated because of funds made available in the FY 1995 appropriation. This initiative focuses upon the biology of age-associated changes and pre-disease conditions in blood vessels. Current research is rapidly expanding our understanding of vascular disease, such as atherosclerosis, and provides directions for the development of new interventions. There is a growing excitement about the potential for preventing and/or alleviating vascular disease by targeting proteins such as advanced glycation endproducts (AGE) as well as using drugs such as taxol to stabilize microtubule function.

Many of our nation's elderly suffer or face death due to diabetes and its complications. A major initiative in NIA's intramural laboratories is underway to develop the basis for novel therapies that would be safe and specific for older diabetic patients. NIA scientists have discovered that certain hormones, normally present in the gut, can restore beta cell responsiveness to glucose and increase insulin effects on insulin sensitive tissues. To investigate new approaches to therapy, studies on the treatment of the beta cells with these hormones and their effects on skeletal muscle, a major site of insulin resistance, are being actively pursued.

NIA is supporting a number of major clinical initiatives that address the burdensome effects of physical frailty and the loss of independence, which often results in the need for long-term care. Ongoing studies have provided convincing evidence of the benefits of exercise for maintaining independent function in older persons. Two studies have demonstrated the efficacy of specific interventions to improve strength in frail older persons and prevent up to 30 percent of all falls. These studies have received widespread attention from the public and from health care providers, and have begun to influence health care practices for older persons which could markedly lower the rate of disabling injuries, especially hip fractures.

Osteoporosis is a major contributor towards physical frailty and the loss of independence. Five clinical studies recently funded will determine the contributions of age and ovarian hormone status to changes in bone mass as women approach and cross menopause. Other studies will explore underlying mechanisms whereby menopause-related changes accelerate bone remodelling and adversely impact upon bone mineral metabolism. Future progress in the prevention and treatment of osteoporosis clearly requires an expanded knowledge of the pathophysiology of this disorder. In particular, NIA will seek to support research studies to determine the most appropriate methods for studying the biology of the aging human skeleton. Such an approach will permit us to understand the nature of the age- and menopause-related changes that lead to bone loss. Related to this research direction is NIA's Women's Health and Aging Study which is exploring the causes and course of physical disability, including osteoporosis, in women aged 65 and older.

BUDGET

Mr. Stokes: To what extent will the FY 1996 budget allow the institute to begin to implement the opportunities that are ready to be exploited?

Dr. Hodes: The NIA will attempt to capitalize on research areas that show continual advancements. This is occurring at the same time that numbers of older Americans continue to grow along with a recognition of the importance of research on aging and its associated diseases.

The NIA is currently engaged in a collective planning effort to determine scientific areas of maximal need and to identify opportunities. It should be noted that NIA has a strong commitment to support the basic research needed to develop a fuller understanding of the fundamental biological processes of aging. Once the mechanisms of aging are understood, the interactions between aging and disease will yield preventive measures and treatments for the disorders that accompany aging. The ultimate goal of aging research is not simply to prolong life but to make the remaining years of life as active, productive and satisfying as possible. To this end, NIA's program of research is designed to develop the knowledge base needed for new methods that can treat and prevent illness and disability, promote independence, and avoid institutionalization.

At a time when resources are limited, efforts continue for rigorous control of the quality of science and the pursuit of excellence in each of these program areas. During a period of growth several years ago, the NIA established a network of research centers designed to support development of grantee institutions as active centers of research on multiple aspects of aging. Fortunately, the projects supported have given us the basis of productivity and promise often needed to stimulate private support to complement ongoing support by the Institute.

CANCER AND THE ELDERLY

Mr. Stokes: What is the extent of cancer in the elderly population? With respect to cancer in the elderly, what are the implications of the recently discovered p53 tumor suppressor gene, and that of the protein that inhibits the cdk2 enzyme discovered by your researchers?

Dr. Hodes: As population-based tumor registry data from the National Cancer Institute reveals, old age is the "normal time" at which cancer develops. The elderly experience the major impact of cancer and have a risk of developing cancer that is 10 times greater than that for individuals younger than 65. The incidence rate for those aged 65 and older is 2,085.3 per 100,000 as compared with 193.9 per 100,000 for those younger than 65. Overall, 58 percent of all cancer incidence is in the older segment of the population. Cancer mortality in the elderly now accounts for 67 percent of all cancer deaths. Compared with the rest of the population, these individuals suffer disproportionately from the morbidity, adversity, and hardship brought on by these malignancies. Furthermore, the older age group has been underrepresented historically in clinical studies that generate knowledge about cancer treatment.

Cancer results when the positive (promotes proliferation) and negative (inhibits proliferation) factors which control cell proliferation become unbalanced in favor of the positive factors. Two of the negative factors are the p53 and p21 proteins. The synthesis of the p21 protein, which inhibits cdk2, requires the product of the p53 gene to be present. Thus, factors which down-regulate the expression of either one of these genes may increase the cancer risk, while factors which up-regulate expression may decrease the cancer risk. Research is continuing to understand how the expression of these genes is regulated, with hope that strategies to appropriately up-regulate these genes in cancer tissue can be developed.

Mr. Stokes: What are the implications of these findings for AIDS, and breast and prostate cancer?

Dr. Hodes: Any strategy for up-regulating the expression of the p21 and p53 genes in cancer tissue would have immediate benefit for treating both breast and prostate cancer, especially if the up-regulation can be directed specifically to the breast or prostate tissues. The relevance of such intervention for treating AIDS is less direct. The intervention would be useful in treating the secondary events associated with AIDS, e.g., Kaposi's sarcoma, but probably would not directly prevent the proliferation of the AIDS virus itself.

TELOMERASE

Mr. Stokes: It has been brought to my attention that the work on "Telomerase" which relates to cancer, has just been named by the Harvard Medical Letter as one of last year's 10 most important advances in medical research, and I recall that the institute has supported some research in this area. Why is this work relevant to aging research?

Dr. Hodes: Age-related changes in cellular gene expression play an important and central role in biological aging. It is possible that specific genes determine how many times a cell divides or proliferates and that the end of cell division, known as senescence, helps determine certain aspects of aging. Hence, life spans and aging may be linked to the limit on cell division. Conversely, when the limit on cell division is removed, as it is for presently unknown reasons in cancer cells, the cells continue growing indefinitely.

It appears that telomeres influence the very basic functioning of cells, including the stability of chromosomes, the ability of genes to be expressed, and ultimately the ability of cells to replicate. It has been found, for example, that each time human or animal cells divide they tend to lose telomeres from the ends of chromosomes. This is known as "shortening." This observation has led NIA investigators to believe that, if cell senescence is indeed one of the fundamental mechanisms of aging, as some biologists speculate, then aging itself may be the flip side of the cancer coin, the byproduct of a mechanism that prevents cells from growing into tumors.

When shortening reaches a critical point in normal human cells, cell division stops. This provides one of many checkpoints that prevent unlimited growth and replication of cells. Conversely, cancer cells do not experience telomere shortening with each cell division. This finding represents a potential solution to the puzzle: if cells stop dividing as telomeres get shorter and shorter, how could one ever have a cancer cell? It appears that the enzyme telomerase provides cancer cells with a means to avoid this normal checkpoint.

By supplementing the ends of chromosomes with bits of DNA, telomerase can successfully reverse the shortening of telomeres that normally occurs with cell division, thus allowing cancer cells to divide in an unregulated manner. Further molecular and genetic studies of telomeres and telomerase are therefore of potential importance for the understanding of both aging and cancer.

AIDS RESEARCH

Mr. Stokes: To what extent has knowledge gained in your AIDS research and breast and prostate cancer research had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your institute?

Dr. Hodes: Research in one area very commonly leads to advances in areas that seem on the surface to have little relation to the primary study. An interesting example of this "spin-off" has resulted from studies on breast and prostate cancer in younger and older rats and mice. While the incidence of these cancers increases with age in the animal model, as it does in the human, the rate of growth of the cancers that develop is slower in the aged animal model. These studies have provided insights into the understanding of normal aging processes on the one hand, and surprisingly, into studies of osteoarthritis as well. Tumor extracts have been found which stimulate cartilage formation; these extracts differ in their effectiveness depending upon the age of the animal from which the tumor extracts were isolated. Extracts from the tumors of young animals were more effective than those isolated from the tumors that grew in old animals. New strategies to improve tissue regeneration have been suggested by these results.

AIDS is caused by a virus-induced loss of T-lymphocytes which are necessary for a robust immune response. T-lymphocyte function also decreases with increasing age in healthy humans. Thus, understanding the impact of loss of immune function on general health in AIDS patients will provide insight into the impact of the age-related loss of immune function in older people, and vice versa. Similarly, understanding the loss of control of cell proliferation in cancer, including prostate and breast cancer, also provides insight into the balance between positive and negative control factors in cellular senescence and a variety of pathological conditions related to increasing age, e.g. cardiovascular disease.

Behavioral research on AIDS has been especially useful for elucidating factors associated with the adoption and modification of health beliefs and behaviors. The behavioral interventions developed for AIDS-related behaviors can be applied to a host of other difficult-to-change behaviors such as stopping smoking, altering diets, or dealing with aggressive behaviors within family units. For example, AIDS research underscores the importance of paying attention to the social context in changing undesirable health behaviors, suggesting that all involved parties should be the targets of intervention efforts rather than the more typically employed individually based interventions.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years? Explain.

Dr. Hodes: From 1985 to 1989, the success rates for NIA competing applications ranged from 24 to 28 percent. In 1990, the success rate dropped to 22 percent, and then climbed to 30 percent in 1991, a year in which the NIA budget was increased by 35 percent. Since 1991, the success rate has ranged from 23 percent to 29 percent.

Beyond fluctuations in a given year in the number of applications received, and the total budgetary resources available to fund research projects grants, success rates will fluctuate because of the cyclical nature of the grants funding process.

Mr. Stokes: What has been the trend in average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Hodes: The table below displays the trends in the average costs of research project grants in both current and constant dollars. It should be noted that fluctuations in average costs are often a result of the same factors that impact success rates.

Average Costs (dollars in thousands)

Fiscal Year	Current Dollars	Constant Dollars
1985	$ 171	$ 171
1986	177	170
1987	194	177
1988	201	174
1989	212	174
1990	220	172
1991	242	180
1992	255	181
1993	264	181
1994	280	185

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African-Americans? From HBCU's?

Dr. Hodes: Because Federal mandates require that questions related to race and gender be identified as optional on all NIH research grant applications, we do not have accurate information from which to determine success rates for minorities and women. In recent years, up to 25 percent of NIA's grant applicants chose not to submit this optional information.

NIA receives very few applications from HBCU's. For example, NIA received an average of slightly over four applications per year for the last six years; in a recent year NIA received just one application. For this reason, success rate data are not meaningful.

It should be noted that the NIA has encouraged research at HBCUs by holding regional meetings around the country to disseminate information about our programs to which HBCU faculty have been invited. Many HBCUs are members of the Association for the Development of Gerontology in HBCUs, and NIA interacts with this organization. Many of the universities, however, are involved in research activities related to service delivery and are more appropriately supported by the Administration on Aging than NIA.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women? To minority researchers? To African-American researchers? To HBCU's?

Dr. Hodes: For the reasons stated above, it is not possible to provide accurate or meaningful data on average costs for these groups of applicants.

DIABETES

Ms. Lowey: I am interested in the work you are conducting on the relationship between diabetes and older patients. Could you discuss the new therapeutic approaches to diabetes that you are exploring?

Dr. Hodes: As age advances, the ability of the body to utilize glucose declines. This decreased metabolic efficiency can be confused with the diabetic state which is similarly characterized by a decrease in the efficiency of handling glucose. Since diabetes is a disease with devastating consequences (coronary heart disease, blindness, kidney failure, gangrene), differentiating the disease from the effects of "normal aging" is a critical question. The NIA has therefore been investigating this issue in several ways:

a. In order to understand the physiological mechanisms underlying this dilemma, NIA intramural scientists developed the "glucose clamp" technique, a method now used world-wide to study metabolic problems in human beings. Basically it allows the quantification of insulin secretion by the pancreas in response to a rising blood glucose level. In addition it provides a measure of the sensitivity of the cells of the body to the insulin that is produced or that is given to patients under treatment.

b. An epidemiologic approach, quite different from the experimental method of the "clamp," has been to study the men and women enrolled in the Baltimore Longitudinal Study of Aging (BLSA). Data from that study are the most comprehensive available in the world on risk factors and predictors that lead to the development of diabetes as individuals age. These data have been important in the planning of a trial for the prevention of the type of diabetes that occurs in mature individuals. The BLSA data are now under intense analysis in order to define better the diagnostic standards used to diagnose diabetes in middle and old age.

Despite the development of new techniques for the administration of insulin and of medications taken orally for the treatment of diabetes, it must be admitted that control of the disease at this time is far from ideal. We are working on two approaches that show great promise. Our approaches are based on the fact that production of insulin by the diabetic patient is deficient. The replacement of insulin by various routes of administration does not accurately mimic the normal secretion pattern of healthy individuals. One approach is to study the effects of hormones normally produced in the intestinal tract ("incretins") that stimulate the secretion of insulin when the blood glucose concentration is elevated. The role of one of these incretins, GIP, in human beings was proven in the IM program several years ago. Another and probably more effective incretin, GLP, is now under study for potential future therapeutic usage.

Another approach is to increase the duration of action of insulin on the cells and tissues of the body and thereby to enhance its effectiveness. Insulin that circulates in the blood stream must first become attached to highly specialized areas on the surface of the cells of the body called "receptors" which become activated when insulin attaches to them. These activated receptors are deactivated by removal of phosphate by an enzyme (tyrosine phosphatase). Control of this specific phosphatase would prolong the duration of action of insulin and thus have the same effect as providing more insulin. A group of highly specific blocking agents which act only on the insulin system are currently being developed. Cloning of novel tyrosine phosphatases has already been accomplished. These studies will possibly provide new pharmacological compounds to treat the older diabetic patient.

PREVENTION

Ms. Lowey: I am aware that NIA supports research on preventing the need for long-term care or institutionalization. Can you tell the subcommittee about this research? What role does NIA play? And what results is the research yielding? How can we keep people out of long-term care?

Dr. Hodes: NIA is supporting research that helps us understand what enables some people with disabilities to live in the community while others with the same level of disability require institutional care at great public expense:

- Data from the longitudinal National Long Term Care Survey showed that the disability rate of the 65 and over population had declined between 1982 and 1989, to the extent that there were between seven and eight hundred thousand fewer disabled older people in 1989 than might have been projected from 1982. The dynamics for this change appear to be related to increased use of assistive devices combined with improved health. Understanding the reasons for the underlying improvement should help accelerate this welcome trend and is a priority to the NIA.

- Recent findings from an NIA-supported National Survey on Self-Care Behaviors that shows how older people with chronic illnesses and disabilities can compensate for their health problems by changing the way they do things, altering their living environments, or using special devices and equipment. The most successful strategies will be disseminated to older people and their families to prevent excess use of health services and unnecessary institutionalization.

- NIA has also targeted research on home health care as a priority research area and is currently funding a pilot study to test the commercial feasibility of converting existing unused living spaces into health care suites for frail elderly relatives who need extra assistance that is most readily provided by and accepted from younger family members. This new form of flexible housing enables older people to live with some degree of independence yet receive needed health care assistance, all at a minimum of capital outlay.

- NIA is also supporting a clinical study designed to evaluate the cost effectiveness of outpatient geriatric evaluation and management to reduce hospital and nursing home admissions of older people with chronic conditions. This study will also evaluate the effectiveness of geriatric case management (assessment and treatment of conditions associated with age related conditions -- falls, frailty) for improving quality of life and survival.

- The Institute also supports research on forecasting how the future demand for long term care will increase as the older population expands. Included in these efforts are attempts to model the dynamics of this process, especially for the oldest old, the fastest growing component of the older population. These efforts are crucial to developing sound long term care policies and programs.

WOMEN'S HEALTH AND AGING STUDY

Ms. Lowey: I understand that NIA's Women's Health and Aging Study is exploring the causes of physical disability, including osteoporosis, in women aged 65 and older. Can you update us on the study? What are we learning about the causes of older women's disabilities?

Dr. Hodes: The Women's Health and Aging Study is a longitudinal study of women 65 years and older with moderate to severe disability. The central objective is to characterize and evaluate factors associated with disability and need for long-term care through comprehensive data collection focusing on medical conditions, physiological and functional decrements and psychological, quality of life and social issues.

Field work to recruit and enroll women representing the approximate one-third most disabled women living in Baltimore, Maryland, commenced in November 1992. In January 1995 the baseline interview and examination were completed for the entire study population of 1,004 women.

Comparing the frequency of chronic conditions in women screening into the study versus those who did not screen-in (the non-disabled), it is clear that several forms of heart disease and stroke, diabetes, arthritis, and respiratory conditions and vision and hearing problems contribute substantially to disability. History of hip fracture is more than twice as high in the disabled population as in non-disabled older women.

The contribution of osteoporosis to disability in older women is as yet unknown. From the baseline data it is evident that its role is not insignificant. Over 16 percent of study participants report that they have been told by a physician that they have osteoporosis, yet less than one-third of these women report current treatment for this condition. Well over 20 percent of this moderate to severely disabled population report a history of any osteoporotic-type fracture and over one-third of the oldest old have a history of osteoporotic fracture. In addition, this population exhibits a high vulnerability for future fracture. Over 35 percent of the total study population report falling in the past year with over 50 percent of the most severely disabled sustaining a fall.

Because the most severely disabled often reside in nursing homes and other long-term care facilities, the prevalence of disease observed in the community-dwelling population underestimates the contribution of chronic conditions to disability. Only through careful longitudinal followup can we better understand the full impact of osteoporosis and other chronic conditions of old age on the health and well-being of older women. The study plans are for a 3-year followup of all participants.

NURSING

Ms. Lowey: I know that NIA has worked in collaboration with the Nursing Institute. Could you tell us about that collaboration? I am a strong supporter of greater use of the expertise of nurses--and am interested in the Institute's work.

Dr. Hodes: In the area of Alzheimer's disease, the NIA and the National Institute for Nursing Research (NINR) issued a joint solicitation for pilot and feasibility studies for new and innovative methods for managing the behavioral symptoms associated with Alzheimer's disease. Some of the areas covered by these studies included assessment of behavioral symptoms and instrument development, management of disruptive behaviors during bathing, physical aggression, vocally disruptive behaviors, agitation, and pacing and wandering. In another joint effort, and in conjunction with support from the Fisher Medical Foundation, NIA and NINR held an Alzheimer's disease planning meeting at which NIA and NINR-funded investigators and others involved in behavioral management studies assessed the state of knowledge and began discussions of the need for larger studies of specific interventions.

In other areas of aging, NIA collaborates with NINR on several ongoing program announcements (e.g., aging and formal health care, women's health over the life course, and Alzheimer's disease: issues in caregiving). NIA also works closely with NINR staff on several multi-site coordinated efforts in diverse areas such as long-term care and minority aging, reducing frailty and injuries in later life, and women's health, aging, and menopause. NIA obtains valuable nursing expertise through nursing input into research agenda setting workshops, suggestions for nurse advisors and reviewers, as well as joint management of collaborative research projects. Similarly, NIA staff are often requested to join NINR activities in order to provide more expertise on health and aging (e.g., NINR Task Force on Long-Term Care).

The Laboratory of Behavioral Sciences of our Intramural Program has developed highly cost-effective behavioral treatment programs for elderly persons living in the community and for elderly residents of nursing homes. These treatments for incontinence are now being implemented throughout the world and, in most settings, the prime provider is a nurse. Further developments of effective techniques in this area have been expanded by collaboration between NIA and the NINR. A scientist (Nurse-Ph.D.) from NINR has been detailed to the Gerontology Research Center to evaluate the relative effectiveness of pelvic floor exercises, estrogen treatment, and a combination of these in the alleviation of the symptoms associated with incontinence.

The addition of our own research nurses has provided a small staff for the investigation of the role of potential nursing behavioral interventions in the facilitation of recovery from hip fracture. We are testing the possibility that such interventions will reduce the incidence of institutionalization of these patients, an unfortunate but very common aftermath of this event. Early results of our studies show that aggressive nursing intervention during the acute period of hospitalization could improve function and increase independence at discharge.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

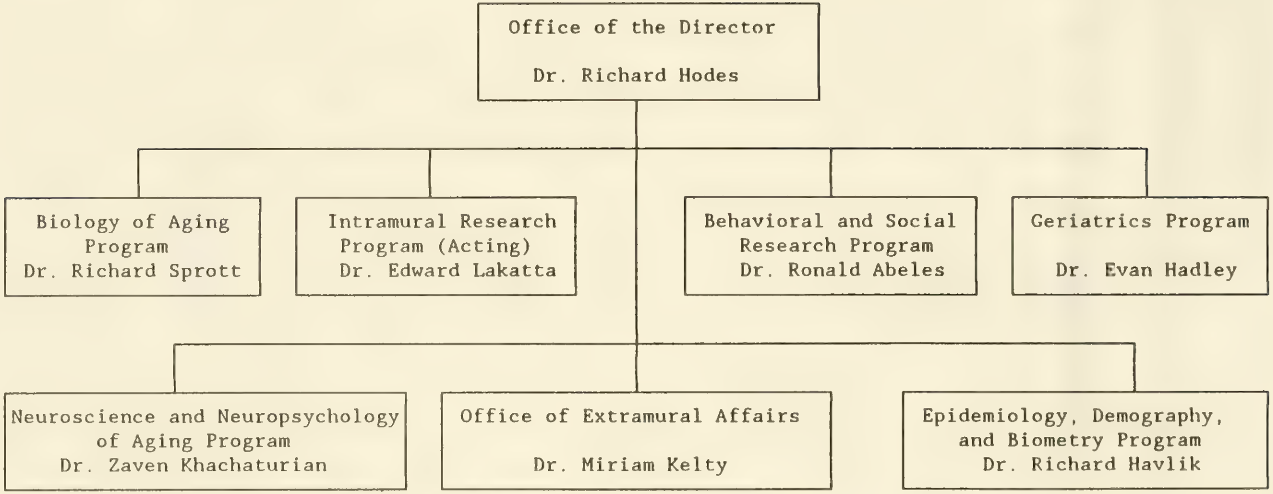
FY 1996 Budget	Page No.
Organization chart	122
Appropriation language	123
Amounts available for obligation	125
Budget mechanism table	126
Summary of changes	128
Budget authority by object	130
Administrative costs	132
Significant items in House and Senate Appropriations Committee Reports	133
Authorizing legislation	134
Appropriation history	135
Budget authority by activity	136
Justification:	
A. General statement	137
B. Extramural research	140
C. Intramural research	150
D. Research management and support	153
E. Detail of full-time equivalent employment (FTE)	154
F. Detail of end-of-year employment	155

122

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to aging, [$432,698,000] *$445,823,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$420,303,000	$432,698,000	$445,823,000
Section 205 Procurement reduction......................		-233,000	
Section 207 Rent reduction........		-2,000	
Section 513 S&E reduction.........		-140,000	
Subtotal, adjusted appropriation...............	420,303,000	432,323,000	445,823,000
Comparative transfer to:			
Office of AIDS Research, NIH for HIV activities..................	-1,686,000		
Comparative transfer from:			
Other NIH Institutes for Management Fund adjustment......	+674,000	+542,000	
Subtotal, adjusted budget authority...........	419,291,000	432,865,000	445,823,000
Unobligated balance lapsing.......	-37,000	----	----
Total, obligations...........	419,254,000	432,865,000	445,823,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1994--$5,790,000; 1995--$5,500,000; 1996--$5,500,000

Also excludes funding for HIV activities: FY 1995--$1,715,000; FY 1996--$1,785,000, included in Office of AIDS Research, NIH.

Note: Excludes $3,700 for royalties in FY 1994 and $11,673 in FY 1995.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants						
Research projects:						
Noncompeting	663	$188,540,000	655	$192,444,000	617	$192,274,000
Admin. suppl	(96)	3,675,000	(42)	2,309,000	(46)	2,601,000
Competing						
Renewal	66	25,451,000	65	30,468,000	69	31,000,000
New	157	32,313,000	147	31,725,000	184	40,070,000
Supplemental	14	1,832,000	13	1,773,000	15	2,290,000
Subtotal, competing	237	59,596,000	225	63,966,000	268	73,360,000
Subtotal, res. proj	900	251,811,000	880	258,719,000	885	268,235,000
SBIR/STTR	45	5,594,000	62	7,621,000	63	7,971,000
Subtotal, res. proj	945	257,405,000	942	266,340,000	948	276,206,000
Research Centers						
Spec./comp. ctrs	61	54,260,000	63	56,920,000	63	56,920,000
Other research						
Res. career program	115	9,170,000	124	10,547,000	124	10,853,000
Minority biom. res		872,000		907,000		933,000
Other res. related	34	3,102,000	40	2,496,000	40	2,568,000
Subtotal, other res	149	13,144,000	164	13,950,000	164	14,354,000
Total, research grants	1,155	324,809,000	1,169	337,210,000	1,175	347,480,000

Training						
Individual awards:						
Noncompeting	16	402,000	28	738,000	21	537,000
Competing	20	525,000	8	154,000	15	408,000
Subtotal, individual	36	927,000	36	892,000	36	945,000
Institutional awards:						
Noncompeting	331	8,317,000	354	9,568,000	371	10,043,000
Competing	103	2,974,000	82	2,092,000	65	2,320,000
Subtotal, institutional	434	11,291,000	436	11,660,000	436	12,363,000
Total, training	470	12,218,000	472	12,552,000	472	13,308,000
Research & development contracts	44	21,907,000	44	22,169,000	42	22,169,000
	FTEs		FTEs		FTEs	
Intramural Research	284	37,881,000	281	38,426,000	276	39,733,000
Research management and support	164	22,476,000	163	22,508,000	163	23,133,000
TOTAL	448	419,291,000	444	432,865,000	439	445,823,000
Clinical Trials		(13,062,000)		(11,260,000)		(8,480,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Summary of Changes

1995 Estimated budget authority	$432,865,000
1996 Estimated budget authority	445,823,000
Net change	+12,958,000

	1995 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
Changes:				
A. Built-in:				
1. Intramural				
a. Within-in grade increases		$19,402,000		+$246,000
b. One more day of pay		19,402,000		+71,000
c. Annualization of January 1995 pay increase		19,402,000		+156,000
d. January 1996 pay raises		19,402,000		+311,000
e. Payment for centrally furnished services		5,074,000		+47,000
f. Increase for service and supply fund		2,092,000		+64,000
g. Increased cost of laboratory materials & other supplies		11,858,000		+373,000
Subtotal				+1,268,000
2. Research Management & Support:				
a. Within-in grade increases		10,063,000		+152,000
b. One more day of pay		10,063,000		+39,000
c. Annualization of January 1995 pay increase		10,063,000		+81,000
d. January 1996 pay raises		10,063,000		+171,000
e. Federal employees compensation fund, unemployment compensation		10,063,000		+3,000

Summary of Changes--continued

	1995 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
f. Payment for centrally furnished services......		2,717,000		+181,000
g. Decrease for Working Capital Fund............		345,000		-9,000
h. Decrease for FTS 2000				-22,000
i. Increase for service and supply fund.........		1,362,000		+42,000
j. Increased cost of laboratory materials & other supplies........		8,366,000		+259,000
Subtotal...............				+897,000
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting...........	655	194,753,000	-38	+122,000
b. Competing..............	225	63,966,000	+43	+9,394,000
Subtotal.................	880	258,719,000	+5	+9,516,000
2. SBIR/STTR.................	62	7,621,000	+1	+350,000
Subtotal.................	942	266,340,000	+6	+9,866,000
3. Research centers...........	63	56,920,000	0	0
4. Other research.............	164	13,950,000	0	+404,000
5. Training...................	472	12,552,000	0	+756,000
6. Contracts..................	44	22,169,000	-2	0
	(FTEs)		(FTEs)	
7. Intramural.................	281	38,426,000	-5	+39,000
8. Research Management and Support...............	163	22,508,000	0	-272,000
Subtotal.............				+10,793,000
Total Changes.........				+12,958,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Full-time equivalent employment......	444	439	-5
Full-time equivalent of overtime and holiday hours..................	3	3	0
Average SES salary...................	$111,688	$113,721	+$2,033
Average GS grade.....................	10.1	10.1	0
Average GS salary....................	$44,759	$45,507	+$748
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207).	$84,817	$86,216	+$1,399
Average salary of ungraded positions.	$29,470	$29,956	+$486
Personnel compensation:			
Full-time Permanent................	$16,553,000	$17,124,000	+$571,000
Other than full-time permanent......	4,367,000	4,516,000	+149,000
Other personnel compensation........	730,000	763,000	+33,000
Special personnel service payments..	2,492,000	2,650,000	+158,000
Total, personnel compensation.....	24,142,000	25,053,000	+911,000
Personnel benefits..................	5,201,000	5,390,000	+189,000
Benefits for former personnel........	122,000	122,000	0
Travel and transportation of persons.	475,000	495,000	+20,000
Transportation of things............	100,000	100,000	0
Rental payments to GSA...............	1,100,000	1,100,000	0
Rent, communications, and utilities..	3,850,000	3,973,000	+123,000
Printing and reproduction...........	315,000	315,000	0
Other Services:			
Consulting services.............	115,000	115,000	0
Other services..................	7,255,000	7,181,000	-74,000
Purchases from Govt.accts........	24,854,000	25,423,000	+569,000
R&D Contracts....................	9,900,000	9,900,000	0
Subtotal, other services..........	42,124,000	42,619,000	+495,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Supplies and materials................	3,275,000	3,469,000	+194,000
Equipment.............................	2,303,000	2,303,000	0
Grants, subsidies, & contributions....	349,762,000	360,788,000	+11,026,000
Insurance claims & indemnities........	96,000	96,000	0
Interest & dividends..................	0	0	0
Total budget authority by object....	432,865,000	445,823,000	+12,958,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

132

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging
Administrative Costs

	FY 1995 Current Estimate	FY 1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	$16,553,000	$17,124,000	+$571,000
Other than Full-time Permanent (11.3)	4,367,000	4,516,000	+149,000
Other Personnel Compensation (11.5)	730,000	763,000	+33,000
Special personnel service payments (11.8)	2,492,000	2,650,000	+158,000
Total Personnel Compensation (11.9)	24,142,000	25,053,000	+911,000
Civilian Personnel Benefits (12.1)	5,201,000	5,390,000	+189,000
Benefits to Former Personnel (13.0)	122,000	122,000	0
Travel (21.0)	475,000	495,000	+20,000
Transportation of things (22.0)	100,000	100,000	0
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities, and Miscellaneous Charges (23.3)	3,850,000	3,973,000	+123,000
Printing and Reproduction (24.0)	315,000	315,000	0
Other services:			
Consulting services (25.1)	115,000	115,000	0
Other services (25.2)	7,255,000	7,181,000	-74,000
Purchases from Govt.accts (25.3)	10,850,000	11,419,000	+569,000
Subtotal, other services	18,220,000	18,715,000	+495,000
Supplies and materials (26.0)	3,275,000	3,469,000	+194,000
Total	55,700,000	57,632,000	+1,932,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1995 House Report	
Alzheimer's Disease	
1. House Report 103-553, page 57, states: "Having identified ApoE as a risk factor in a substantial proportion of Alzheimer's patients, NIA is extending studies to determine the role of ApoE and other defined gene products in the pathology of this disease. The Committee encourages NIA to accelerate its research in this field."	1. NIA expects that it will continue to receive quality grant applications on ApoE related research that can be funded, and will pursue ApoE related work through both the intramural research and contract support mechanism.
1995 Senate Report	
Alzheimer's Disease	
1. Senate Report 103-318, page 92 states: "The Committee understands the NIA is considering altering its Alzheimer's disease centers and satellite centers program...The Committee believes that now is not the time to alter the centers grant program and directs the Institute to withhold alterations during fiscal year 1995."	1. The NIA will continue support to the Alzheimer's disease centers and satellite centers program, and anticipates that approximately the same number of awards will be funded for FY 1995.
Nursing	
2. Senate Report 103-318, page 93, states: "The Committee urges the NIA to continue to work collaboratively with the National Institute of Nursing Research (NINR) to address research issues involving nursing practice in the process of the aging population."	2. The NIA continues to have a positive collaborative relationship with the NINR in promoting research on the care and management of the aging population.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Authorizing Legislation

	PHS Act Other Citation	U.S. Code Citation	1995 Amt. Authorized	1995 Appropriation	1996 Amt. Authorized	1996 Budget Request
Research and Investigation.............	Section 301	42§241	Indefinite	$420,313,000	Indefinite	$432,515,000
National Institute on Aging..................	Title IV, Part C	42§289k-2 - 289k-5	Indefinite		Indefinite	
National Research Service Awards...........	Section 487(d)	42§288	Such sums as necessary	12,552,000	Such sums as necessary	13,308,000
Total Budget Authority......				432,865,000		445,823,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$145,829,000	$174,279,000	$179,582,000	$177,681,000
1988	156,174,000	203,411,000 2/	199,642,000	194,746,000
1989	204,770,000	225,578,000	210,222,000	222,643,000
1990	229,620,000 3/	241,528,000	245,490,000	242,685,000 4/
1990 Sequester				-3,230,000
1991	248,938,000	278,311,000 5/	377,733,000	323,752,000 6/
1991 Sequester				-4,000
1992	348,558,000	362,528,000	397,176,000	383,382,000 7/
1993	407,284,000	402,218,000	405,218,000	399,924,000 8/
1994	394,156,000	420,303,000	420,303,000	420,303,000
1995 9/	433,701,000	430,968,000	432,968,000	432,323,000 10/
1996 9/	445,823,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ House Allowance consolidated all AIDS activities in OASH.

3/ The 1990 request excludes funds for the National HIV program ($870,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes enacted administrative reduction of $824,000.

5/ Excludes $9,520,000 in NRSA training programs not considered.

6/ Excludes enacted administrative reductions of $8,020,000 and $1,010,000.

7/ Excludes enacted administrative reductions of $120,000, $2,783,000, and $729,000.

8/ Excludes enacted administration reductions of $3,236,000, $162,000, and $1,146.000.

9/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

10/ Excludes enacted administration reductions of $233,000, $2,000, and $140,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Estimate		1996 Estimate		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Extramural Research												
Aging...............	---	$323,366	---	$337,021	---	$358,934	---	$371,931	---	$382,957	---	+$11,026
Intramural.............	290	36,721	305	38,259	284	37,881	281	38,426	276	39,733	-5	+1,307
Research Management and Support.........	187	21,723	167	23,090	164	22,439	163	22,508	163	23,133	0	+625
Total, obligations....	477	381,810	472	398,370	448	419,254	444	432,865	439	445,823	-5	+12,958
Unobligated balance lapsing.............	---	---	---	+8	---	+37	---	---	---	---	--	---
Total, Budget Authority...........	477	381,810	472	398,378	448	419,291	444	432,865	439	445,823	-5	+12,958

Justification

National Institute on Aging

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
448	$419,291,000	444	$432,865,000	439	$445,823,000	-5	+$12,958,000

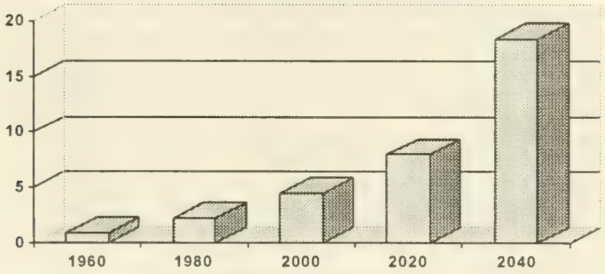
General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute on Aging (NIA). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Congress created the NIA in 1974 as part of the National Institutes of Health. At that time, aging research was just in the early stages of developing ways to explore the fundamentals of the aging process. Now, over 20 years later, the science base has grown in depth, breadth, and detail. And with this growth has come new insights into the processes and the experience of aging.

Driving an increasing interest in aging research is a projected dramatic increase in the older population. People over 65, who were four percent of the U.S. population in 1900, will constitute approximately 13 percent in the year 2000 and 20 percent by the year 2025. The over-85 age group is the fastest growing segment of the American population and is often referred to as the "oldest old". This boom in the population of older Americans will have a profound impact on the Nation's health, social, and economic institutions.

PROJECTIONS OF U.S. POPULATION:
85 AND OLDER (in millions)



Projections from Bureau of Census Data.

Research in aging over the last two decades has contributed to the realization that aging should not be equated with inevitable decline and disease. Consider Alzheimer's disease (AD): This form of dementia has now been linked to alterations in specific proteins and has been shown to affect specific regions of the brain. As a result, it is no longer possible to think of AD as "senile dementia," an old term which implied that losing one's memory was simply part of growing older. Part of this new perspective has its roots in the use of new technologies to explore the fundamental biology of aging. Where researchers once theorized about the causes of growing old, they now have the means--in recombinant DNA techniques and nuclear magnetic resonance, for instance--to track down the actual mechanisms of aging in cells and tissues. Once the mechanisms of aging are understood, the interactions between aging and disease will yield to preventive measures and treatments for the disorders that often accompany aging.

Fueling the growth of this science are increasingly important links between aging research and other areas of biomedical and behavioral investigation. For example, the study of aging cells now overlaps substantially with research on the cellular mechanisms of cancer and cardiovascular disease. Similarly, the study of the aging brain now has numerous intersections with basic neurobiology and research on brain disease. Increasingly, research on aging has become an integral part of mainstream health research.

Even with the hope of major advances in the treatment and prevention of debilitating diseases, the demand for long-term care is expected to expand in our society. Research will be conducted on many aspects of long-term care, particularly on new and evolving forms of care. NIA supports research on preventing the need for long-term care or institutionalization, enhancing the quality and efficiency of such care, easing the burden of long-term care, and forecasting the requirements for long-term care.

Alzheimer's disease is a top research priority for NIA. It currently affects an estimated four million older Americans and their families, causes enormous personal suffering, and costs the nation billions of dollars each year. NIA devotes over $200 million annually to Alzheimer's disease research. Without the development of new treatments, cures, or preventive approaches to this dreaded disease, the number of individuals and families devastated by Alzheimer's disease will likely increase up to five-fold within the next 50 years. In addition to Alzheimer's disease, priority initiatives include research on the biology of the aging process and on physical disabilities such as osteoporosis and cardiovascular disease. These initiatives are wide-ranging and can be based on cutting-edge laboratory technologies or upon simple but highly effective strategies such as exercise or behavioral interventions. The goal of NIA-supported research is to understand the basic mechanisms of normal aging and age-associated disease and disability and to translate this basic knowledge into treatment and prevention strategies.

The President's appropriation request of $445,823,00 for this account represents current law requirements. No proposed law amounts are included. Funding levels for the National Institute on Aging for the last five years has been as follows:

	Amount	FTE
FY 1991	$322,827,000	438
FY 1992	381,810,000	477
FY 1993	398,378,000	472
FY 1994	419,291,000	448
FY 1995	432,865,000	444

Purpose and Method of Operation

The NIA funds extramural awards through the Aging activity, and operates an intramural research program. Extramural support is funded either through research grants, research training grants, or research contracts. An award mechanism of particular importance to NIA is the research center. NIA center programs are developed in concert with Congressional directives to fill research needs in areas such as Alzheimer's disease, physical frailty, demography, or rural health and aging.

Overall Budget Policy

The NIA FY 1996 request is $445,823,000, an increase of $12,958,000 or 3.0 percent over the comparable FY 1995 level of $432,865,000. The FY 1996 budget will provide $276,206,000 for approximately 948 research project grants. Approximately 268 new and competing research project grants will be awarded. The FY 1996 request provides $56,920,000 to fund 63 research centers; $14,354,000 to fund 164 other research awards; and $13,308,000 to support 472 full-time training positions. The FY 1996 request also includes $22,169,000 to fund 42 research contracts; and includes $39,733,000 for intramural research and $23,133,000 for research management and support. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

National Institute on Aging

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$358,934,000	$371,931,000	$382,957,000	+$11,026,000

The research activities described within this section are extramurally funded through NIA grants and contracts awards.

Funding levels for the extramural Aging activity during the last five years have been as follows:

	Amount
FY 1991	$270,567,000
FY 1992	323,366,000
FY 1993	337,021,000
FY 1994	358,934,000
FY 1995	371,931,000

Rationale for the Budget Request

With the FY 1996 extramural request, these funds will provide support for the Aging activity of $382,957,000, an increase of $11,026,000 or 3.0 percent over the FY 1995 estimate of $371,931,000.

BASIC RESEARCH ON AGING

Caloric Restriction and Biomarkers of Aging

As aging becomes more and more a topic of public concern, interest in interventions to delay or eliminate the consequences of aging has grown enormously. Although the molecular processes that must be responsible for species-specific rates of aging are poorly understood, the gross physical and physiological manifestations of aging are well characterized in many species. The differences in these aging changes within and between species suggest that aging is a multi-process phenomenon. As a result, chronological age is not a good predictor of physiological or functional age. Better measures of physiological or functional age are known as "biomarkers of aging." The NIA is currently in the seventh year of a ten year initiative to develop a set of biomarkers of aging which could be used as measures of aging-related biological changes in experimental systems and in human beings.

It has been known since early this century that caloric restriction extends the lifespan of rodents; useful biomarkers of aging might predict the life extension that results from caloric restriction. Studies conducted so far show that caloric restriction retards the development of virtually all age-related lesions and tumors, reduces oxidative damage to neurons and slows the decline in the immune system associated with aging. An understanding of how caloric restriction produces this effect would provide important insights into preventive measures and therapies to retard and/or alleviate the effects of aging. The NIA and the FDA have sponsored more than 30 groups to conduct research on biomarkers and caloric restriction. Currently, they are in the final stages of testing in rodent models prior to considering their translation to human studies.

The Roles of Oxidative Damage and Programmed Cell Death in Aging

Oxidative damage to critical cell components is chronic and ubiquitous in living cells. Although extensive repair systems exist in these cells, repair is never 100 percent complete. The purpose of this initiative is to determine: 1) what factors regulate the amount of damage incurred by cells, 2) what factors regulate the repair of this damage, 3) whether unrepaired damage contributes to aging, 4) the role of cell suicide in eliminating damaged cells, and 5) whether interventions can be developed to retard aging. Recent research results by NIA grantees include the following:

- long-lived nematode (round worm) mutants express increased levels of antioxidant defense enzymes, and higher levels of antioxidant enzymes in fruit flies extend maximum life span.
- when "ß-amyloid" protein, which accumulates in the brains of patients with Alzheimer's disease, is placed in solution it generates reactive oxygen capable of killing neurons through oxidative damage.
- mice carrying one or more extra copies of the antioxidant defense enzyme "superoxide dismutase" are more resistant to oxidative stress compounds which induces diabetes in animal models.

When oxidative stress overwhelms the cellular defense and repair systems, an alternative protective strategy for the organism is for the damaged cell to actually commit suicide. Whereas this may be the best way to eliminate a heavily damaged and potentially cancerous liver cell, the elimination of a neuron has more serious consequences because of the inability to replace lost neurons. Thus, an understanding of how cell death is regulated may be crucial not only in preventing cancer, but also in preventing neurodegenerative disease. Recent research results by NIA grantees include the identification of several genes required for induction of the programmed cell death pathway.

Cellular Senescence

It is possible that specific genes determine how many times a cell divides or proliferates and that the end of cell division, known as senescence, helps determine certain aspects of aging. Most cells are limited in the amount of times they can divide; a built-in barrier to unlimited growth. This limit is higher in longer-lived species, such as humans, than in shorter-lived species. Hence, human cells can proliferate more times than mouse cells. This and other observations have led to speculation that life spans and aging may be linked to the limit on cell division.

Cellular senescence intrigues researchers for another reason: While on one hand it limits life span, it may also prevent cancer. When the limit on cell division is removed, as it is for presently unknown reasons in cancer cells, the cells continue growing indefinitely. If cell senescence is indeed one of the fundamental mechanisms of aging, as some biologists speculate, then aging itself may be the flip side of the cancer coin, the byproduct of a mechanism that prevents cells from growing into tumors. Whatever the "purpose" or end result of cell senescence, the genes that regulate it are the focus of intense study. NIA-supported scientists in several laboratories have already isolated genes that seem to promote cell proliferation--called oncogenes --and other genes that seem to stop proliferation, often referred to as tumor suppressor genes. Understanding why and how these genes are "turned on" or expressed may uncover new pathways for understanding both aging and cancer.

It has been found, for example, that each time human or animal cells divide, there is a loss of DNA from the ends of each chromosome. The ends of chromosomes are called "telomeres". When telomeres have shortened beyond a critical point, cells can no longer divide and are senescent. This mechanism would limit the amount of cell division that any cell can undergo, potentially limiting life span but also providing protection against the uncontrolled cell division that occurs in cancer. Recent analysis, however, has shown that an enzyme called telomerase can reverse telomere shortening in some normal cells such as sperm cells, as well as in cancer cells where telomerase allows cancer cells to continue uncontrolled division. Further molecular and genetic studies of telomeres and telomerase are therefore of potential importance for the understanding of both aging and cancer, and will be supported by NIA.

Gene Therapy

Whereas aging results from both genetic and environmental factors, appropriately designed genetic interventions may be able to slow aging due to both kinds of factors. For example, increased expression of genes for antioxidant enzymes might be effective in reducing damage due to oxidative stress in specific tissues. If specific age-related degenerative changes can be delayed by genetic intervention, high quality of life can be maintained, and health care costs can be delayed until later in life. This will be of particular benefit if the period of time ultimately spent in ill health can be shortened, and if the severity of the loss of function can be attenuated, thus reducing overall health costs.

For example, it is well known that wound healing declines with age. An NIA grantee is carrying out basic studies to determine what factors are limiting wound healing in aged animals. He has developed a protocol to test whether treatment of tissue with transforming growth factor by injection along the line of the incision prior to surgery improves wound healing. Preliminary results with another cytokine show a temporary increase in wound strength. Such studies offer great potential if they could be applied to the elderly undergoing elective surgery. This research is also attempting to develop a safe and effective method for introduction of the gene coding for cytokine DNA into the tissue around wounds.

Mechanisms of Neuronal Cell Dysfunction

Understanding why brain cells become dysfunctional and die in older persons is of primary concern to NIA; elucidating the underlying causes could lead to new therapeutic strategies to delay, correct, or prevent the loss of these vital cells and the resulting neurological deficits. Research into mechanisms of nerve cell death and the compensatory response of central nervous system cells has been recently stimulated by NIA. Critical to an understanding of some of the neurodegenerative diseases may be the link that impaired energy metabolism could have with nerve cell death. NIA will also encourage research on protein transport and signal transduction at the nerve cell membrane. Study of the components essential for membrane function will provide information on how the specialization of nerve cell surface is constructed, but even more importantly, will show how it may change leading to a variety of neurodegenerative diseases as well as the conditions such as cognitive decline normally associated with aging.

Sensory and Sensory-Motor Dysfunction

Visual and hearing impairments are present in respectively about 10 and 32 percent of American adults aged 65 years and older. The somatosensory areas of touch, temperature, pain, and motion are also important to successful aging but have received even less attention than studies of visual and hearing dysfunction. All too often older individuals have more than one sensory impairment. Because individual researchers tend to focus work on the study of one sense or another, questions about neural mechanisms that may be common to sensory processing and/or sensory dysfunction have not been explored adequately. The NIA stimulates multimodal sensory research, addressing questions such as the contribution of sensory processes to the control of balance, posture, and locomotion, areas of importance because impairments can severely compromise the mobility of older adults. Falls in older adults, which account for almost all of the 250,000 hip fractures occurring annually and commonly result in long-term disability, may be due in large part to impairments in these sensory systems.

ALZHEIMER'S DISEASE

Alzheimer's disease will reach critical proportions in the U.S. and other countries as the population ages. We are now faced with a major public health crisis if something is not done to halt the progress of this dreaded disease. Since the prevalence of Alzheimer's disease increases dramatically with age after about 65 years, delay of the onset of Alzheimer's disease by five years would substantially reduce the number of cases, and a delay of ten years would largely eliminate the disease in the normal human lifespan. Several exciting recent genetic discoveries have shed new light on the etiology and pathogenesis of Alzheimer's disease. Recently, apolipoprotein E4 (ApoE4), a blood protein whose gene is located on chromosome 19, has been shown to be associated with greatly increased risk of Alzheimer's disease. This extremely important observation has been confirmed in a number of laboratories and is the first report of a major biological risk factor of the disease. In addition, there are many laboratories currently involved with trying to identify the gene on chromosome 14 associated with early-onset familial Alzheimer's disease. Other important studies in the etiology area include extensive analysis of the cellular, genetic, and molecular parameters of nerve cell function in health and in disease. Such basic research will provide a necessary understanding of the molecular underpinnings of Alzheimer's disease. Alzheimer's disease research has been of paramount importance at NIA since the Institute came into existence. To conquer the disease and to bring urgently needed support to patients, families, and researchers, NIA has built a nationwide framework for research and assistance. The structure includes:

- **Alzheimer's Disease Centers (ADCs).** Located at major medical institutions around the country, the 28 ADCs are collecting and studying longitudinal data on the disease; working to translate research advances into clinical services; and educating and training professionals. Satellite centers in rural and remote communities are recruiting minority participants into the Centers' programs.

- **Drug Discovery Groups.** Located at six research centers, these groups are designing, developing, and testing new drugs aimed at delaying, halting, or reversing the progress of Alzheimer's disease. These groups focus on drugs at the pre-clinical stage, before testing in people.

- **Cooperative Study Units.** These 32 research sites are conducting cooperative clinical studies (i.e., in people) of drugs developed by the Drug Discovery Groups and other projects. The first study to assess the effectiveness of Deprenyl plus Vitamin E in slowing the course of the disease began in October, 1992. Another study, for drug and behavioral treatment of agitation began in June, 1994, and a study of the anti-inflammatory drug prednisone for treatment of Alzheimer's disease began in November, 1994. A conference was held in 1994 to evaluate the state-of-the-art in behavioral management in Alzheimer's disease, and to discuss the possibility of initiating larger-scale studies.

- **Alzheimer's Disease Education and Referral Center (ADEAR).** This clearinghouse with its toll-free number (800-438-4380) is a central source of information on all aspects of the disease. During calendar year 1994, 82,022 calls were received.

- **Consortium to Establish a Registry for Alzheimer's Disease.** This network is working to establish uniform standards for diagnosis to facilitate early and accurate detection of the disease and support research.

- **National Cell Repository.** This growing repository of blood samples from Alzheimer's disease patients facilitates the study of genetic defects associated with the disease.

A major theme in Alzheimer's disease is to extend knowledge about the age incidence, prevalence rates, and risk factors. The search for risk factors in minority and other distinct population groups could lead to better understanding of the pathophysiology of Alzheimer's disease and novel treatments. These ideas have been the underlying themes for three sets of studies that have been completed over the past year. One group of researchers conducted an incidence study of dementia in relation to education and occupation and found that the risk was greatest for individuals with both low education and low lifetime occupational attainment. A study by another group, done in pairs of older twins, has indicated an apparent inverse relationship of Alzheimer's disease with sustained exposure to steroidal and, possibly, non-steroidal anti-inflammatory drugs, suggesting that these agents may prevent or delay the symptoms of Alzheimer's disease. A third study found that the risk of developing Alzheimer's disease decreased significantly with increasing dose and duration of estrogen replacement therapy, suggesting that estrogen deficiency may be one of the factors that elevates a woman's risk of developing the disease. Estrogen replacement therapy may be useful for both symptomatic treatment and preventing or delaying the onset of dementia in susceptible postmenopausal women. After further preliminary research, clinical trials of anti-inflammatory drugs and estrogen may be initiated.

The clinical diagnosis of Alzheimer's disease has improved as the result of work of many investigators. In specialized research facilities, clinical diagnosis by research neurologists and psychiatrists now approaches 90 percent concordance with the subsequent neuropathological diagnosis. However, there remain important questions and gaps in knowledge. A major area in the development of new noninvasive diagnostic procedures has been that of imaging using Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), and Magnetic Resonance Spectroscopy Imaging (RSI). These kinds of techniques hold the promise of early diagnosis of Alzheimer's disease and the ability to monitor, non-invasively, the course of the illness.

CLINICAL, APPLIED AND BEHAVIORAL RESEARCH

Influenza Vaccine

Influenza, commonly known as the flu, can be a very serious and often life-threatening illness in older persons. An NIA-supported study demonstrated the efficacy of an improved influenza vaccine in approximately 400 nursing home residents. Half of the participants received the commercially available influenza vaccine (HA) and the other half received an influenza vaccine against the same flu strains, but which was linked to another vaccine component, diphtheria toxoid. Clinical surveillance of all participants for respiratory illness was performed twice weekly for 5 months. During an outbreak of influenza, fewer diphtheria-toxoid-linked vaccine recipients than HA vaccine recipients had laboratory-confirmed infection. Of these recipients, fewer of the diphtheria-toxoid-linked vaccine-treated participants had bronchial and lung infections. The investigators concluded that the toxoid-linked vaccine produced greater protection from influenza infection for institutionalized elderly recipients. NIA will continue to support studies of basic cellular and molecular immunology in order to better understand the changes in immune function that occur with aging as well as clinical research because of the potential of improving vaccines for a variety of infections in older persons.

Physical Frailty

NIA is supporting a number of major clinical initiatives that address the problems of physical frailty and loss of independence associated with older persons. Physical frailty is a major cause of need for long-term care and imposes annual costs of billions of dollars. Results from ongoing studies provided convincing evidence of the benefits of exercise for maintaining independent function in older persons. Some interventions from a clinical trial on frailty and injuries have shown more than a 30 percent reduction in fall rates, which could markedly lower the rate of disabling injuries such as some hip fractures. Two studies have demonstrated efficacy of interventions to prevent falls and improve strength in frail older persons. Both have received widespread attention from health care providers and the public and have begun to influence health care practices for older persons.

One study employed a "targeted intervention" strategy for frail community-dwelling subjects with a variety of risk factors for falls. The subjects received individualized treatment for their particular risk factors including medication adjustments, strength and balance training, instruction on safe practices to avoid lightheadedness and environmental hazards, and training in specific activities such as getting in and out of the bathtub. Over a one-year follow-up period, the treated subjects had 44 percent fewer falls per year than the control group who received social visits only.

In another controlled study of frail nursing home residents, it was found that a ten-week resistance exercise program approximately doubled leg strength, increased walking speed by 11 percent, improved stair-climbing power by 28 percent, and led to increased spontaneous physical activity. This study also found that supplementing the diet with protein and calories had no effect alone and no significant additional effect when combined with exercise.

Menopause and Aging

There is little consensus on the significance of menopause in healthy aging or on its role in the chronic diseases/disorders of old age such as cardiovascular disease, osteoporosis and urinary incontinence. Not surprisingly, considerable controversy exists over the scope of the physiological changes surrounding menopause or that appear later in life that are attributable to reduced ovarian function *per se*. Menopause is a universal phenomenon; however, the manifestations of menopause are not. Cross-cultural research demonstrates considerable variability between populations in symptom presentation and associated psychosocial and physiological effects of these symptoms.

In order to gain an increased understanding of the inter-relationship between menopause and disorders such as osteoporosis, cardiovascular disease, and the other chronic diseases and disorders of old age, NIA began a major research initiative in this area in 1994. Future success in preventing and managing diseases and disorders which impact on post-menopausal women will require a substantially improved knowledge base to differentiate the contribution of "hormone deficiency" from that of aging. Advances can do much to clarify ambiguities in the presentation of age-related disease, improve diagnosis and treatment, and ultimately reduce health care costs. Similar considerations also apply to age-related changes in other endocrine factors, such as growth hormone and testosterone.

NIA also continues to support the NIH Women's Health Initiative, which includes 70,000 post-menopausal women ages 50-79. This study is intended to assess the long term benefits and risk of hormone therapy as it relates to cardiovascular disease, osteoporosis, and breast and uterine cancer. Related to this effort is NIA's Women's Health and Aging Study which is exploring the causes and course of physical disability in women aged 65 and older. The study will provide important information on how the disease-disability relationship is modified by cognitive functioning; on psychological factors; and on social, economic, and medical resources of older women.

Osteoporosis

Osteoporosis and its consequences, particularly vertebral and hip fractures, are a significant cause of frailty, morbidity, and even mortality in old age. NIA-supported osteoporosis research includes clinical studies of age-related bone loss and fracture epidemiology, intervention trials to prevent or reverse bone loss, studies of skeletal biology and the effects of sex steroids and growth factors on bone cell function. Five clinical studies recently funded will conduct prospective longitudinal studies to determine the contributions of age and ovarian hormone status to changes in bone mass as women approach and cross menopause. Some studies will explore underlying mechanisms whereby menopause-related changes accelerate bone remodelling and adversely impact on bone mineral metabolism.

Future progress in the prevention and treatment of osteoporosis clearly requires an expanded knowledge of the pathophysiology of this disorder. In particular, NIA will seek research studies to determine the most appropriate methods for studying the biology of the aging human skeleton. Such an approach will permit us to understand the nature of the age- and menopause-related changes that lead to bone loss. In addition, it will facilitate the identification of risk factors for, and specific markers of, the occurrence or reversal of bone loss, which will be valuable in identifying the potential of response to treatment, and/or monitoring the course of treatment.

Biology of Age-related Muscle Weakness (Sarcopenia)

Although a number of studies have noted correlations of age-related changes in muscle properties with disability and metabolic impairments, considerable gaps in our knowledge are still present. With respect to outcomes, muscle weakness in the extremities contributes to loss of functional independence and falls. However, we still know little about 1) which age-related changes in specific muscle properties (e.g., mass, isometric strength, isokinetic strength, rate of torque development, fiber type distribution, fatiguability) significantly affect function and performance of specific tasks (walking, maintaining balance, etc.), and 2) what level of changes in muscle properties is required to significantly affect function.

Age-related changes in muscle properties may also contribute to non-insulin dependent diabetes mellitus, osteoporosis, risk for fracture, impaired fracture healing rates, and risk for hypo- and hyperthermia. Clarifying these relationships, including their quantitative aspects, would reveal much about the pathologic significance of these changes in muscle and their overall health impact.

Self-Care And Aging

NIA is currently supporting research on the nature, extent, and outcomes of self-care behaviors in diverse populations of older people in order to develop social and behavioral interventions for encouraging health and effective functioning in later life. While health surveys have indicated that most older people engage in some form of self-care behavior, there has been a lack of specification in these prior surveys. NIA is now documenting the wide variability in older people's self-care practices, specifying factors associated with engaging in particular self-care behaviors (e.g., self-management for chronic health conditions and self-care practices to compensate for functional limitations affecting routine activities of everyday living). Such specifications are important for documenting the links between particular self-care practices and illness or disability.

Inappropriate self-care can lead to delays in seeking needed care or conversely, overutilization of the medical care system for trivial symptoms. Recent NIA studies on medical self-care dispel myths that suggest older people are incapable of recognizing the significance of illness symptoms and that they are more prone than younger persons to use inappropriate strategies that could exacerbate conditions. While most older people have a good knowledge of symptoms and risks, NIA studies show there is a need for greater health education regarding the causes and consequences of common non-specific symptoms (such as fatigue, sleep difficulties, headache, and stomach pain), which are often erroneously attributed to age or stressful situations. Future research initiatives are being planned to develop a better understanding of the complex processes involved in care-seeking and to suggest ways to better interpret symptoms and self-treatment.

Minority Aging And Long Term Care

Dramatic increases are expected in the number of non-minority older people, 92 percent by the year 2030; but the projected growth in the older minority population--over 250 percent by 2030--points to a need for research on aging in minority populations. NIA has increased its funding of minority-relevant research projects from $5 million in FY 1990 to an estimated $30 million in FY 1995 because of the critical need for scientific information on ethnic older people. Recent comparisons show that with comparable levels of frailty, African-Americans are less likely to enter nursing homes or enter at older ages than non-minorities. Other findings are that family care is more common than the use of formal care for all minorities, and that recent immigrants are least likely to be institutionalized. Future studies, however are challenged by the need to disentangle the influence of cultural preferences for home or institutional care from the effect of socioeconomic differences for the largely disadvantaged older minority population. Understanding these and other ethnic variations in long term care has significant implications for structuring of formal services and assisting the possibly cost-effective alternative of continued family care.

Cognitive Factors In Everyday Functioning Of Older People

NIA supports research on social, behavioral, and biological factors affecting cognitive functioning as people age. More recently, efforts are being directed at the implications of declines in cognitive functioning for older people's ability to perform daily tasks, such as driving, decision-making, and understanding and following medical instructions. Of particular importance for such tasks are changes in "attentional resources"--the ability to identify and process relevant information simultaneously from multiple sources. While older people perform less well in general on tasks requiring divided attention, expertise in or familiarity with the task considerably lessens older people's disadvantage. Research has confirmed that older people have greater difficulty than younger people in understanding written medical instructions. However, how the information is presented can have a significant impact upon comprehension. For example, older people can more easily understand instructions presented as a list as opposed to paragraphs. Taken together, these and other research projects highlight the practical implications of basic cognitive research for the daily lives of older people. For example, those older people who suffer deficits in visual attention are at greater risk for automobile accidents. NIA research has shown that through proper training and practice, these deficits can be overcome or lessened.

Demography of Population Aging

Population aging will become one of the most important social phenomena of the next half century, especially when the babyboom generation becomes eligible for Social Security and Medicare. How this nation and its institutions accommodate themselves to the dramatic demographic age-shift will have a significant effect on the quality of life in the twenty-first century. NIA-supported research in the field of demography of aging can be characterized by an orientation towards intergenerational relations, especially within the family; and a focus on the characteristics and behaviors of older people themselves, especially in the critical areas of economics and health. To further these goals, NIA recently funded nine Demography Centers to promote the use of data from national surveys of health, retirement, and long-term care by the larger research and policy-making communities. The field of "biodemography" is emerging, which integrates biological and genetic research with demographic methods, and which should enable a better understanding of how to forecast life and health expectancies.

Research progress in the demography of aging is currently being made in several areas. According to NIA-funded studies, it is evident that the rate of increase in human mortality slows after age 95; possibly even declining after age of 110, and that centenarians are the fastest growing age group. The findings emerging from this body of research are increasingly being used to inform actuarial estimates for the Social Security and Medicare Trust Funds. One interesting study of a small group of nuns suggests that persons who earn college degrees and constantly challenge their minds, are likely to live longer and suffer less from dementia. One hypothesis explaining this finding is that education builds a greater "brain reserve capacity" which can better compensate for the affects of neurological disorders.

The Health and Retirement Study (HRS), which follows persons aged 51-61, has completed the second interview wave. The HRS will be used to study topics such as the influence of health and private pensions on retirement, the impact of changing Social Security's age of eligibility provisions, and the impact of the Americans with Disabilities Act. The Asset and Health Dynamics of the Oldest-Old study, which follows persons age 70 years and over to examine the interplay of family and economic resources and late life health transitions, has completed the first wave of data collection; analysis is underway.

National Institute on Aging

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
284	$37,881,000	281	$38,426,000	276	$39,733,000	-5	+$1,307,000

The Intramural Research Activity supports research conducted by government scientists in Baltimore, Maryland and at the NIH Clinical Center, as well as the operation of NIA's Epidemiology, Demography, and Biometry Program and also supports the post-doctoral training of promising investigators in the intramural laboratories.

Funding for the Intramural Research Activity for the last five years has been as follows:

	Amount	FTE
FY 1991	$33,118,000	271
FY 1992	36,721,000	290
FY 1993	38,259,000	305
FY 1994	37,881,000	284
FY 1995	38,426,000	281

Rationale for the Budget Request

The FY 1996 budget request for Intramural Research is $39,733,000, an increase of $1,307,000 over the FY 1995 estimate of $38,426,000.

Intervening in Aging Processes

The causes of aging are complex and involve both environmental and internal factors that damage molecules, cells, and tissues and the ability of the host to resist and repair such damage. NIA scientists, using the latest techniques of molecular and cellular biology, are making significant progress in elucidating mechanisms that underlie aging processes and in devising ways to retard and reverse age associated deficits. Findings and related opportunities include the following. 1) A commonly occurring mineral has been shown to inhibit programmed cell death (apoptosis) of endothelial cells following removal of growth factors and to improve the angiogenic response in aged animals. This may be a useful strategy to restore the growth of blood vessels in degenerative diseases of aging. 2) Chondrocytes (cells responsible for production of cartilage) can be induced to divide in culture by treatment with growth factors and then stimulated to reform cartilage when injected back into mice. This lays the foundation for cell-based repair of cartilage defects that are common in age associated disease of cartilage. 3) NIA scientists developed techniques to measure DNA damage and its repair in the telomeres (end regions of chromosomes that decay with aging) and recently demonstrated that repair declines with age. 4) The isolation of factors from old animals that inhibit blood vessel formation and tumor growth is ongoing. Analysis of spontaneous rat breast tumor cells may yield insights into the loss of suppressor gene function in the progression of breast cancer.

Baltimore Longitudinal Study of Aging (BLSA)

The BLSA, begun in 1958, seeks to understand how and why we age. At this stage of its evolution, health outcomes are accumulating and participants, now numbering over 1,170, have been followed for significant segments of their lives. A BLSA DNA bank is being established; enabling protocols on apoE risk and protective factors in cognitive aging and on preferential DNA repair in breast cancer to proceed. BLSA studies also explore the role of risk factors for health and longevity, such as obesity, glucose and insulin metabolism, and plasma cholesterol. Each of these has been shown to continue to play a role into very old age, but the definition of "normality" for each must be age-specific. Prevention efforts depend upon accurate definition of risk, and such data are becoming uniquely available through the BLSA. A ten year BLSA study of the causes and natural history of prostate cancer, benign prostatic hyperplasia (BPH) and normal prostatic growth in Caucasian and African-American men continues. The BLSA Perimenopausal study is an intensive evaluation of 100 Caucasian and 100 African-American women who will be seen four times each year until menses have ceased for two years or hormone replacement is begun. Age-matched men, premenopausal women and older postmenopausal women already enrolled in the BLSA provide contrast groups to assess the separate effects of sex and estrogen status on normal aging.

Alzheimer's Disease (AD)

The IRP has a focused research program on the etiology, diagnosis and treatment of AD. Scientists have shown that overexpression of mutant forms of the amyloid precursor protein (APP), which have been implicated in AD, correlates with a reduced rate of capillary tube formation when cells are grown in culture and leads to enhanced cell death in differentiated neuronal cells. These results suggest new approaches for AD treatment involving reducing the expression of APP and intervening in the cell death pathway induced by APP. Also, recent studies suggest that apolipoprotein E (apoE) is a risk factor for AD and that the apoE4 gene is more frequent in AD patients. IRP scientists are relating apoE4 genotypes of BLSA participants to repeated cognitive assessments made over the past 30 years. As this research continues, apoE genotypes will be related to normal and pathological rates of cognitive changes, especially risks for developing AD.

Vascular Disease

The ongoing intramural effort on age associated vascular disease will continue to capitalize on recent advances. These include the finding that the injury-transformed vascular smooth muscle cell, which is largely responsible for the vascular blockage in restenosis--renarrowing of an artery following angioplasty or balloon dilation--is critically dependent on intact microtubule function. Intramural scientists have found that taxol, a potent microtubule stabilizing agent, prevents this vascular narrowing by 70-80 percent in an animal model without significant toxicity. Others are investigating the potential utility of gene therapy to induce the formation of new blood vessels and enhance collateral blood flow to compromised or damaged heart tissues and to prevent restenosis after coronary artery angioplasty. "Advanced glycation endproducts" (AGE) are proteins that accumulate in the blood stream and blood vessels of diabetic patients and older individuals; these products interact with specific receptors present on circulating blood and blood vessel cells. Intramural scientists, in concert with extramural colleagues, have made a number of recent discoveries that have fueled a growing excitement about the potential role of this system as a novel therapeutic target for preventing and alleviating vascular disease. These include observations suggesting that the signalling pathway activated by this receptor plays an important role in the progression of all vascular disease and that activation of these receptors leads to increased intracellular oxidant stress.

Frailty, Osteoporosis, Hormone Replacement and Women's Health

Issues of women's health and well-being command special attention within the intramural program. Studies are ongoing with models of postmenopausal osteoporosis to determine the efficacy of an analog of the common antibiotic tetracycline in preventing accelerated bone loss. A collaborative clinical trial comparing the effects of growth hormone, sex steroid replacement, and growth hormone combined with sex steroid in men and women over 65 continues; it is expected to provide important new data on the risk benefit ratio of such treatments in older people. Women aged 65-75, treated for two years with constant oral estrogen/low dose daily progestin, showed improved bone mineral density, decreased biochemical evidence of bone resorption, a decrease in percent body fat, increases in lean body mass, and improved cholesterol profiles compared with BLSA controls. A new study of the interactions of treatment with growth hormone releasing hormone with and without estrogen replacement therapy on bone biochemistry and microanatomy in osteoporotic women 55-75 years of age has begun. A National Institute for Nursing Research and NIA study of elderly patients hospitalized with hip fracture suggests that an aggressive nursing intervention during the acute period of hospitalization could improve function and increase independence at discharge.

Diabetes and Other Age Associated Metabolic Defects

Metabolic abnormalities, including type II diabetes, are extremely common in the older population. A major intramural initiative is underway to develop new therapies that are safe and specific for the control of blood glucose in older diabetic patients to prevent the disease's late complications. Molecular approaches are being used to address the factors responsible for type II diabetes--an impaired ability of the beta cells of the pancreas to respond to blood glucose and a decreased insulin responsivity at target tissues--and to elucidate underlying mechanisms. Intramural studies have shown that specific gut hormones can restore beta cell responsiveness in conjunction with glucose and also increase insulin effects on insulin sensitive tissues. To investigate potential therapeutic strategies, studies of the effects of acute and chronic treatments of the pancreatic beta cells with these hormones and their effects on skeletal muscle, a major site of insulin resistance, are being pursued. Emphasis is directed to defining further a region of the insulin receptor that is essential for its activation status to prolong insulin's action. These advances are being aggressively pursued given their promise for opening new therapeutic avenues.

National Institute on Aging

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
164	$22,476,000	163	$22,508,000	163	$23,133,000	-	+$625,000

The research and management support (RMS) activity provides administrative support and scientific management for the grants and contracts awarded under the aging activity, as well as for overall program direction and policy development.

Funding for the Research Management and Support activity during the last five years has been as follows:

	Amount	FTE's
FY 1991	$19,142,000	167
FY 1992	21,723,000	187
FY 1993	23,098,000	167
FY 1994	22,476,000	164
FY 1995	22,508,000	163

Rationale for the Budget Request

The FY 1996 budget request for RMS is $23,133,000, an increase of $625,000 over the FY 1995 estimate of $22,508,000.

The extramural initiatives supported by NIA have been developed and are managed by the extramural program staff funded by the RMS activity. Scientific staff members focus their efforts on developing research initiatives, reviewing, awarding, and administering grants/contracts on aging research and training to universities, hospitals, medical centers, and other organizations. The RMS mechanism also provides funding for facility support costs, related expense items essential to all research programs, and the mandated Alzheimer's Disease Education and Referral (ADEAR) Center which gathers, maintains, and disseminates information on Alzheimer's disease research and services. The center operates a toll-free telephone number to provide the latest information and referral services to health professionals. The NIA has developed a national health education campaign to inform health professionals and the public about the importance of the pneumococcal pneumonia vaccine. Direct support is also provided for the operation of several interagency coordinating committees related to aging research; NIA is chair or co-chair of these committees which include the Federal Forum on Aging, the DHHS Advisory Panel on Alzheimer's Disease, and the Task Force on Aging Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	78	78	78
Biology of Aging Program	12	12	12
Behavioral and Social Research Program	15	15	15
Geriatrics Program	10	10	10
Neuroscience and Neuropsychology	14	14	14
Office of Extramural Affairs	35	34	34
Epidemiology, Demography, and Biometry Program	18	17	16
Intramural Research Program	266	264	260
	448	444	439

Average GS/GM Grade

1991	10.1
1992	10.4
1993	10.3
1994	10.1
1995	10.1
1996	10.1

NOTE: Includes 4 FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute on Aging
Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-4....................	6	6	7
ES-2....................	1	1	1
Subtotal.............	7	7	8
Total - ES Salary.....	$741,200	$781,818	$909,765
GS/GM-15................	28	28	27
GS/GM-14................	33	32	32
GS/GM-13................	28	28	27
GS-12...................	43	42	41
GS-11...................	43	42	42
GS-10...................	1	1	1
GS-9...................	27	27	26
GS-8....................	11	11	11
GS-7....................	45	44	43
GS-6....................	36	36	36
GS-5....................	12	12	12
GS-4....................	6	6	6
GS-3....................	2	2	2
Subtotal............	315	311	306
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director grade...........	17	17	17
Senior grade.............	5	5	5
Subtotal........	22	22	22
Ungraded...........	111	111	110
Total permanent positions....	330	326	321
Total positions end of year....	455	451	446
Total full-time equivalent(FTE) employment, end of year	448	444	439
Average ES level	3.7	3.7	3.8
Average ES salary	$105,886	$111,688	$113,721
Average GS/GM grade	10.1	10.1	10.1
Average GS/GM salary	$43,679	$44,759	$45,507

TUESDAY, MARCH 21, 1995.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

WITNESSES

DR. MICHAEL D. LOCKSHIN, ACTING DIRECTOR
DR. STEVEN J. HAUSMAN, DEPUTY DIRECTOR
MARGARET S. KERZA-KWIATECKI, EXECUTIVE OFFICER
ROBYN J. STRACHAN, BUDGET OFFICER
DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. The subcommittee will come to order.

Our hearings on NIH continue today with NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and their budget request for 1996. And we're delighted to welcome Dr. Michael Lockshin. Dr. Lockshin, why don't you introduce the people at the table with you and then proceed.

INTRODUCTION OF WITNESSES

Dr. LOCKSHIN. Thank you, Mr. Chairman.

To my right is Dr. Steven Hausman, our Deputy Director. To my left, Ms. Margaret Kerza-Kwiatecki, our Executive Officer. And to her right is Ms. Robyn Strachan, our Budget Officer. You know Dr. Kirschstein; you know Mr. Beldon.

OPENING STATEMENT

You have my written remarks for the record. I'd like to highlight some of the major points. First, let me introduce you to NIAMS. NIAMS is the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The A in its name, arthritis, stands for diseases that you all recognize, rheumatoid arthritis, osteoarthritis, and Lyme disease, and diseases that are less well known, such as lupus, fibromyalgia, and scleroderma.

The M stands for musculoskeletal. Musculoskeletal means muscles and bones, orthopaedics. The orthopaedics part of the Institute deals with osteoporosis, Paget's disease, Marfan syndrome and brittle bone disease, hip replacement surgery, healing of bone fractures, exercise medicine and space medicine are also musculoskeletal. The S stands for skin diseases, such as psoriasis, skin ulcers, occupational rashes, baldness, acne and abnormal skin color. It also includes dreadful congenital diseases that blister and scar the skin.

Four words describe NIAMS's diseases: crippling, chronic, common, and costly. Crippling, because these diseases disable their victims totally. Usually they do not kill. And these diseases are important, even though they do not show up in national death rates. Chronic, because they last long times, sometimes lifetimes. Common, these diseases affect children and the elderly, women more than men and all races. One of two women after menopause will suffer an osteoporotic fracture. Four of every five people will suffer low back pain. One in three will have serious skin disease. And costly, there are medical costs, hospital costs, chronic care costs, and lost income costs that continue for years, making them more expensive in the long run than many diseases that do kill.

Now, because the two major diseases, osteoarthritis, which is worn-out joints, and is shown on the right of the poster, and osteoporosis, or weak bones that fracture, shown on the left of the poster, occur after mid-life, the graying of the country means that there will be virtual epidemics of these diseases by the year 2020, only 25 years from now. One of every five Americans, 20 percent of the entire population, half of those over age 65, will have some form of arthritis. Some of you and some of us at this table will be affected. The point I want to make is that NIAMS believes its research can develop the tools to prevent these epidemics. But we can't wait 25 years to start. The time to invest is now.

Here's what we've done recently. Last April, we convened a panel of experts to evaluate research in osteoarthritis. We then asked for grant applications, and we will fund between six and eight of these this summer. We also look forward to initiating a new intramural research program on bone and cartilage. So there will be progress in osteoarthritis. Last September, we held a consensus development conference on hip replacement surgery. The goals of NIAMS are to make hip replacements last a lifetime, or to prevent the need for them altogether. Both of these goals can be achieved.

Osteoporosis, the disease of weak bones, is also a coming epidemic. Last year we found a gene that identifies some women at risk. This year, we have follow-up studies that confirm the importance of this gene and a paper to be published this Thursday in the New England Journal of Medicine that says that we can identify those women most at risk for hip fracture.

Last June, we supported a consensus development conference that recommended optimal amounts of dietary calcium to help prevent osteoporosis. We are about to fund nine new exciting grants on basic research on this disease. NIAMS leads the osteoporosis part of the Women's Health Initiative, and we are particularly pleased that it supports 10 recruitment centers for Latino and Native American and African American women in Texas, Arizona, Alabama and other areas.

Lupus is a serious and severe disease that attacks young women, African-Americans and Latinos more than whites. I'm going to tell you a little story about a woman with lupus. This picture has a very personal meaning to me, and it tells a lot about how NIAMS affects individual lives.

Before joining NIH, I was a New York based physician and researcher. This young lady pictured on the right is one of my patients. I first met her when she was falling into a coma because of brain disease due to lupus. And at that time, she was only 18 years old. At that time, I was supported by a grant from NIAMS to study treatment of brain lupus. She benefited from what we learned, and though it took more than a year, she recovered completely.

A few years later, she fell in love and married. When she and her husband decided to start a family, I was still her doctor, and at that time was supported by a different grant from NIAMS, this time to study lupus in pregnancy. The textbooks at the time said pregnancy was too dangerous for women with lupus to undertake. My work proved the textbooks wrong. But lupus pregnancies are not easy, and little Andre, the baby, was born at six and a half months and weighed just under two pounds. But he was healthy. He is now 10 years old. I talked to his mother a couple of weeks ago, and she told me that he just won a spelling bee in the Bronx. I think actually I'm more proud of that than the parents are.

Your past support of NIAMS did make a very real and continuing difference to this family. Your continued support in the future will make just as much difference to many other families.

NIAMS deals with skin diseases, too. Pictured here are examples of two types of genetic skin disease. People afflicted with such illnesses are ostracized and in pain. Their lives are devastated. The good news is that NIAMS investigators, intramural and extramural, in Bethesda and California and Illinois and other places, have made startling progress in defining the abnormalities that cause many of these diseases. We are on the verge of testing gene therapies that may cure them.

We also look forward to new treatments for many of our other diseases, treatments based on genes for rheumatoid arthritis and lupus and psoriasis and other treatments for skin ulcers and occupational skin disorders.

Most of our cures come from basic research. This picture shows a common cold sore virus. The point of the picture is not the virus, but the basic science, structural biology, which allowed this picture to be drawn. One of our intramural scientists interested not in viruses but in how proteins interact, used space-age technology to take this virus apart and put it together again. He found a target against which drugs can be designed to prevent the virus from attaching to human cells, a very novel way of preventing disease. Thus, basic research still pays off quite handsomely.

I'll conclude by returning to where I began, Mr. Chairman, the diseases represented by NIAMS are crippling, chronic, common, and costly. They will cost this Nation immensely in pain and in dollars in the future. The time to invest in the research is now.

Mr. Chairman, the President's budget request for NIAMS is $235,428,000. Thank you.

[The prepared statement and biography of Dr. Michael Lockshin follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Acting Director

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Mr. Chairman, members of the committee, it is a privilege to appear before you today to discuss the research programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and to share with you some of our advances and initiatives.

The mandate of the NIAMS is diverse. It encompasses diseases that affect the joints, muscles, bones, connective tissue, and skin. These include chronic conditions such as rheumatoid arthritis, osteoarthritis, osteoporosis, Paget's disease, low back pain, psoriasis, and acne. They also include serious diseases of the connective tissue such as scleroderma, epidermolysis bullosa, ichthyosis, and Marfan syndrome. When they strike, the results can be devastating to individuals, to families, and to society.

The diseases within the research scope of the NIAMS are costly. They are chronic and crippling. They destroy the quality of life of those afflicted. Arthritis and musculoskeletal and skin diseases are among the most common causes of chronic pain, disability, and disfigurement in the United States today. They afflict millions of Americans. They draw no boundaries by age, race, or gender. Women, minorities, children, the elderly, and athletes are affected disproportionately.

The cost to society of these diseases is tremendous, both in medical care and lost productivity. According to data compiled by the American Academy of Orthopaedic Surgeons, arthritis costs the Nation $55 billion annually in direct and indirect costs. Add to this equation the expected rise in prevalence as the elderly population increases, and the economic implications are staggering. Estimates from the NIAMS National Arthritis Data Workgroup (NADW) show that, today, one in every seven Americans is afflicted with arthritis. By the year 2020--age 70 for those born in 1950--one in five Americans will have arthritis.

The good news is that we are making progress. Investment in research today will lead to more effective treatments and prevention strategies. Even small advances in critical areas can have a major economic impact. Projections based on the NADW estimates suggest that if we can reduce the burden of arthritis today by only 10 percent, we can save $150 billion in total costs by 2020. The opportunities await, and the time to invest is now.

Osteoarthritis is a disease of major concern to the NIAMS. The prevalence of osteoarthritis increases with age. Thus the number of cases will rise dramatically as the population of this country ages. Osteoarthritis is the most common of all the rheumatic diseases; it currently affects an estimated 16 million Americans and, according to an article in the Journal of Rheumatology, direct costs to the Nation are $8 billion each year. This debilitating disease, which destroys the cartilage of the joints, is the major reason for artificial hip joint replacements.

Hip replacement surgery is extraordinarily successful and cost effective. This was the conclusion of a recent Consensus Development Conference on Total Hip Replacement sponsored by the NIAMS and the Office of Medical Applications of Research. The goal of research remains, however, to lessen the need for hip replacement surgery. To accomplish this, research on the causes and prevention of osteoarthritis is crucial.

The NIAMS, the National Institute on Aging, and the American Academy of Orthopaedic Surgeons convened an expert panel to discuss "New Horizons in Osteoarthritis." The panel recommended future directions for research. The NIAMS and the National Institute on Aging then developed an initiative based on these recommendations, and research grants in response to this initiative will soon start. A separate NIAMS initiative on biomaterials led to new research projects on improved and longer-lasting orthopaedic devices for use in patients with osteoarthritis and other musculoskeletal diseases.

Osteoporosis should be preventable. Nonetheless, it remains the major underlying cause of bone fractures. The disease affects more than 25 million Americans and, according to the National Osteoporosis Foundation, costs the Nation over $10 billion in direct costs annually. In groundbreaking research reported last year, investigators supported by the NIAMS identified a gene that may predict an individual's susceptibility to osteoporosis. This discovery could make it possible to identify, early in life, individuals at high risk for osteoporosis and to initiate prevention programs. Currently, the NIAMS is coordinating efforts to confirm the findings of the first investigators to isolate this gene.

Prevention of osteoporosis depends on building strong bones early in life and avoiding bone loss later in life. One way to build strong bones is through correct diet. The NIAMS sponsored a Consensus Development Conference this year on optimal calcium intake. This panel of experts concluded that Americans of all ages do not now have enough calcium in their diets. The panel recommended an optimal amount of daily calcium for each segment of the population.

The NIAMS plans several initiatives on osteoporosis. As a result of our BONES (Basic Osteoporosis: New Experimental Strategies) initiative, the Institute will fund promising research projects on the cellular, molecular, physiological, and genetic aspects of osteoporosis. While osteoporosis is predominantly a disease associated with women, it also occurs in men. Research on the disease in men is another area in which the NIAMS plans to focus its efforts.

In other areas of importance to the NIAMS, genetics research shows exciting advances in diseases like systemic lupus erythematosus. This is a serious autoimmune disease that disproportionately affects women and African-Americans. Recent studies on the genetics of lupus have brought researchers closer to understanding this and related rheumatic diseases.

New research has uncovered a gene that, when defective, may be responsible for the development of animal and human lupus. This gene controls a process by which the body eliminates unnecessary, damaged, potentially harmful cells. When the gene is defective, harmful cells that would normally be destroyed are permitted to remain in the body where they react against the body's own tissues. Preliminary research suggests that this defect occurs in humans with lupus. Better understanding of this process may lead to new treatments.

To take advantage of these advances and to target areas ripe for development, the NIAMS, the National Center for Human Genome Research, and the Office of Research on Women's Health will convene a panel of national experts. This group will suggest new studies and offer recommendations on prioritizing, coordinating, and funding current genetic studies of lupus.

Improved understanding of lupus, rheumatoid arthritis, and other rheumatic diseases has led to the development of a surge of novel therapies by private sector researchers. To speed this process and link ongoing private sector clinical trials with basic research on lupus and rheumatoid arthritis, the NIAMS is seeking research projects that explain why the novel therapies are effective.

One new treatment approach involves research on the role that angiogenesis plays in rheumatoid arthritis. Angiogenesis is the process by which new blood vessels are formed in tissues, a process which underlies the development of the swollen joints that occur in this disease. In a recent study supported by the NIAMS, researchers produced an inhibitor that blocks angiogenesis in disease models and thus slows or even prevents the disease. The inhibitor is currently the subject of preliminary clinical trials. The NIAMS plans to expand future efforts in this field.

Musculoskeletal fitness and muscle injury are also of great concern to the NIAMS. Repetitive motion injuries, such as carpal tunnel syndrome, and injuries from sports are common in our society. Millions of Americans, from the most sedentary to the most athletic, experience muscle injuries that cause long-term disabilities. Research includes studies on muscle injuries caused by strenuous activity, and on muscle wasting due to inactivity. The NIAMS collaborates with the National Aeronautics and Space Administration (NASA) to study how muscle and bone cells respond to changes in gravity, knowledge which will help recovery of persons who are paralyzed, bed-ridden, or forced to wear a cast.

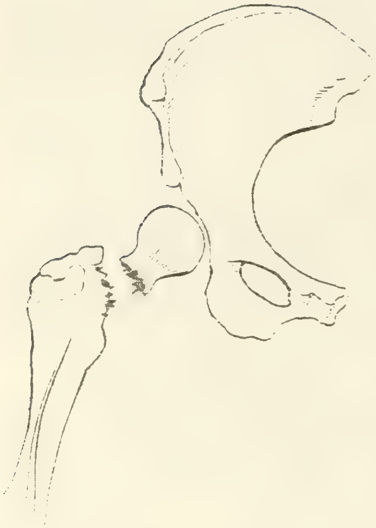
Research on skin diseases is also moving forward. New techniques have enabled scientists to decipher the basic defects in several genetic skin diseases. Epidermolysis bullosa (EB) describes a group of genetic skin diseases which cause blistering in the structure that joins the inner and outer layers of the skin. Using modern genetic technology, investigators have found abnormal genes that cause EB. Similar studies have uncovered the genetic defects in albinism, Marfan syndrome, and Ehlers Danlos syndrome. The techniques of molecular genetics are also used in studies on psoriasis, a common skin disease that affects approximately five million Americans, and the ichthyoses, a group of scaling skin diseases. Gene therapies to combat these potentially devastating diseases are now foreseeable.

Wounds that fail to heal are costly and painful. According to a 1993 article in The Journal of the American Medical Association, the healing of just one bed sore can result in direct costs of as much as $40,000. Bed sores are a major health concern because they commonly occur in elderly and chronically ill individuals. Today, scientists are making progress in understanding how wounded tissue heals; the NIAMS supports this research. In response to a conference on the Pathogenesis of Chronic Wound Healing, the NIAMS developed initiatives to encourage future research in this area. There was great response to these initiatives. Newly funded studies explore ways to translate recent knowledge into effective treatments. Success in this area has the potential for huge savings and major relief from pain and disability.

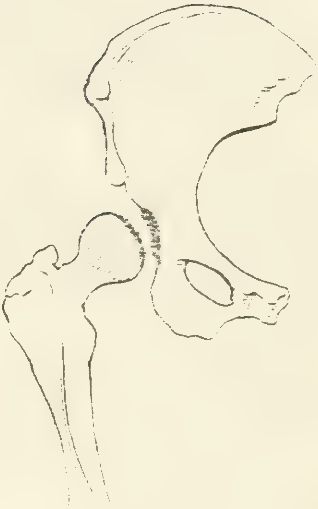
Recent advances in research have led and will continue to lead to better knowledge of and treatments for arthritis, musculoskeletal, and skin diseases. These advances, however, have usually been the result of basic research rather than scientific efforts specifically directed at one disease. Our investments in basic science have paved the way for our best successes. This Institute is committed to foster basic science research through extramural funding and through our Intramural Research Program. Only with continued support of basic science will we prevent and cure the many crippling, costly diseases that affect our Nation today.

Mr. Chairman, the FY 1996 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases is $235,428,000. I will be pleased to answer any questions you may have.

POSTER 1



Osteo**porosis**
(fragile bones)



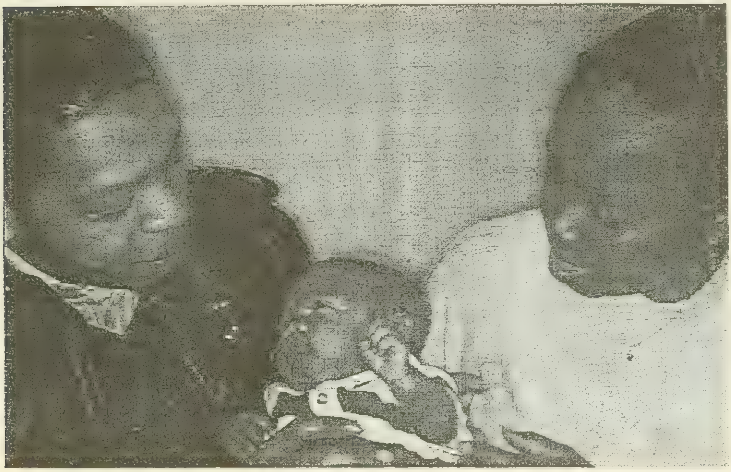
Osteo**arthritis**
(worn joints)

The coming epidemics

Systemic Lupus Erythematosus

Past: 50% died 3 years after diagnosis

Present: 90% survival
Better lives



Future: understanding, control, cure

- Basic science
- Genes
- Women
- Minorities
- Novel treatments

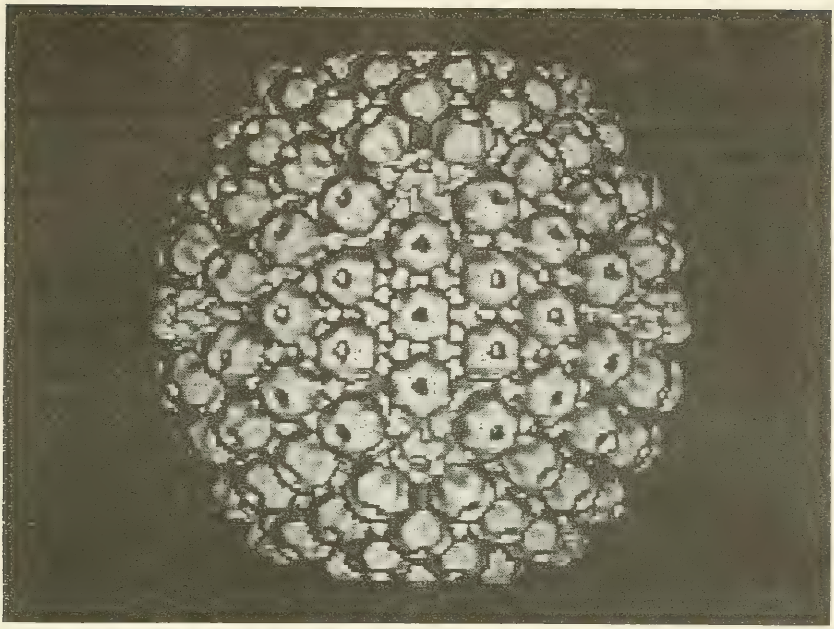
POSTER 2

Genetic Skin Diseases

- Hundreds identified
- Exact cause known for many
- Gene therapy about to begin

POSTER 3

Basic Science



We get our best answers
in surprising ways

POSTER 4

LOCKSHIN, DR. MICHAEL D.

Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

December 9, 1937, Columbus, Ohio

Education: Harvard College, A.B., 1959; Harvard Medical School, M.D., 1963.

Professional History: 1963-64, Intern and Resident, Second (Cornell) Medical Division, Bellevue Hospital and Memorial Hospital for Cancer and Allied Diseases, New York. 1964-66, Epidemic Intelligence Service Officer, Communicable Disease Center, Atlanta, Georgia, and Assistant Professor of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania. 1966-68, Intern and Resident, Second (Cornell) Medical Division, Bellevue Hospital and Memorial Hospital for Cancer and Allied Diseases, New York. 1968-70, Fellow in Rheumatic Diseases, Columbia-Presbyterian Medical Center, New York. 1970-75, Assistant Professor of Medicine and Assistant Attending Physician, The Hospital for Special Surgery, Affiliated with The New York Hospital-Cornell University Medical College, New York. 1976-82, Associate Professor of Medicine and Associate Attending Physician, The Hospital for Special Surgery, Affiliated with The New York Hospital-Cornell University Medical College, New York. 1982-89, Professor of Medicine and Attending Physician, The Hospital for Special Surgery, Affiliated with The New York Hospital-Cornell University Medical College, New York. 1989-present, Director, Extramural Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland. 1994-present, Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland.

Professional Organizations: American Rheumatism Association, including Education Committee (Chairman), Committee on Rheumatologic Practice (Chairman), and Second Vice-President; Arthritis Foundation, including Board of Governors, Professional Education Committee (Chairman), and Unproven Remedies Committee (Chairman); American Board of Internal Medicine: Sub-Specialty Committee on Rheumatology (Chairman); American College of Physicians: Medical Knowledge Self-Assessment Program IX (Chairman); American Board of Medical Examiners: Member for Rheumatology; SLE Foundation of America, Inc.: Medical Advisory Committee (Chairman); Editorial Boards: *Arthritis and Rheumatism, Journal of Rheumatology*, and reviewer for many other journals including *New England Journal of Medicine, Journal of Clinical Investigation, and Journal of Immunology;* American Association for the Advancement of Science; New York Rheumatism Association (Secretary Treasurer, Vice President, President).

Honors, Awards: Invited lecturer and Honorary Member, Sociedad Chilena de Reumatologia, Chile, 1981. Invited lecturer, Sociedad Argentina de Reumatologia, Argentina, 1981. Visiting Professor, Hospital de Clinicas Gaffree e Guinle, Brazil, 1982. Invited lecturer, International League Against Rheumatism, Australia, 1985. Invited lecturer, Pan-American Congress of Rheumatology, Argentina, 1986. Invited lecturer, Sociedad Chilena de Reumatologia, Chile, 1987. Invited lecturer, International League Against Rheumatism, Brazil, 1989. 23rd Annual Harold W. Knowles Lecture, San Francisco, 1989. Co-chairman, Pregnancy in the Rheumatic Diseases Conference, Israel, 1992. Invited lecturer, Fifth International Symposium on Antiphospholipid Antibodies, United States, 1992. J.F.L. Woodbury Lecture, Halifax, 1993. NIH Merit Award, 1993. Invited lecturer, Sixth International Symposium on Antiphospholipid Antibodies, Belgium, 1994. NIH Director's Award, 1994. International Advisory Committee, Fourth International Conference on Systemic Lupus Erythematosus, Israel, 1995. Invited lecturer, Australian Society of Clinical Immunology and Allergy, Australia, November 1995 (pending).

RESEARCH PRIORITIES

Mr. PORTER. Dr. Lockshin, thank you. Yours is one of the newer Institutes at NIH, and you haven't been able to fully establish the research base in all areas of your jurisdiction. Now that we're facing an era of severe budget constraints, are you forced to think about concentrating your resources in a few key areas of strength rather than spreading them too thinly across a broad range of programs?

Dr. LOCKSHIN. Well, Mr. Porter, we have two separate ways of setting our priorities, by the peer review system and by our Advisory Council. And we believe that we set our priorities appropriately across all diseases and across the sciences that we cover through the peer review systems.

So no, we are not looking to cut down by ending our funding of one or another area. If we're forced to cut down, we'll do it by reducing the total amount of research in each of the areas.

TOTAL HIP REPLACEMENTS

Mr. PORTER. Last year, I raised the issue of hip replacements with NIAMS. I understand that your consensus conference determined that this surgical procedure is highly successful, and you alluded to it in your testimony. What progress is being made on the development of biomaterials that are more durable and which would lessen the need for a second hip replacement?

Dr. LOCKSHIN. As you know, we have done two things in the recent past on this particular topic. The first is that we requested applications on biomaterials last year. We funded four separate new grants from that, looking specifically at ways of improving biomaterials.

The second thing that we did is have a consensus development conference on total hip replacements. It did demonstrate that total hip replacements are phenomenally successful surgery, in fact, they were called the most important or the most successful surgery of all the surgical advances, all surgery, in the past 50 years.

But total hip replacements are not permanent. They are now expected to last probably 10 years, possibly more. But what we expect with the new developments that are coming about in biomaterials is that we will look forward to having hip replacements that last 30 years or lifetimes if they have to.

We can see that forthcoming. The final comment that I'll make is that we are engaged in plans for a conference on biomaterials in all of human biology, not just hip replacement, but biomaterials overall. We'll look forward to identifying both the problems and the advantages for those.

Mr. PORTER. Isn't this important to develop longer term materials because isn't surgery of this type more risky as you get older?

Dr. LOCKSHIN. Well, it's risky as you're——

Mr. PORTER. It's hard to do a hip replacement on somebody who's 80 years old or 85 years old, I would think.

Dr. LOCKSHIN. Putting on my physician hat, there's nothing technically more difficult about doing it in an older person than a younger person. But the diseases and the medical experiences the person brings to that surgery are much more, so that both recovery is more difficult and the complications are more difficult.

But hip replacements are put in people just as soon as they've finished growing, sometimes in the late teens. And it's just as important to be able to have those people live perhaps another 50, 60, 70 years with that hip replacement if we can do that.

HYPERTHYROIDISM AND OSTEOPOROSIS

Mr. PORTER. I recall some research being done on the relationship of hyperthyroidism and osteoporosis. Can you tell us about that?

Dr. LOCKSHIN. I think the easiest thing I can tell you is that all disorders of the thyroid, whether it be excess thyroid or under production of thyroid, do affect bone metabolism. And persons with either type of thyroid disease are subject to osteoporosis or to weak bones. Recently there have been a number of things in the newspapers about women with osteoporosis who take thyroid medication on a chronic basis. There's no question that this is true, and it's a problem. The issue is predominantly those women who take it unnecessarily.

CALCIUM INTAKE

Mr. PORTER. You sponsored a consensus development conference on calcium intake, which concluded that Americans of all ages don't receive enough calcium. For the record, can you identify the intake levels recommended by the conference, and what steps did they suggest to increase Americans' consumption of calcium?

Dr. LOCKSHIN. I can give you precisely the numbers, and they differ, according to the person's age and clinical state. Infants from birth to six months are recommended to take 400 milligrams per day; from six months to a year, 600 milligrams per day. Children from 1 to 5 years, 800 milligrams per day. Children 6 to 10 years, 800 to 1200 milligrams per day. Adolescents and young adults, up to age 24, 1200 to 1500 milligrams per day. Men up to the age of 65, 1000; over 65, 1500. Women 25 to 50, 1000 milligrams per day, but if they're pregnant and nursing, 1200 to 1500 milligrams per day. And after 50, if they're taking female hormones or estrogens, 1000 milligrams, and all others 1500 milligrams per day.

Now, these are recommendations for optimal calcium intake, not minimal calcium intake. And they're meant to create the strongest possible bones for preventing osteoporosis. The recommendations made are that persons in the age groups indicated take supplemental calcium. That could be done through fortified fruit juices, it could be done through some diets, and it could be done by taking calcium as either pills or as natural products.

Mr. PORTER. Are there other dietary factors that prevent the assimilation of calcium and its utility for production of bone?

Dr. LOCKSHIN. Yes, that's actually a quite complex science that goes into the absorption of calcium. Certain other metals like magnesium can interfere with calcium. This may not be the forum to go into the details of the specific dietary factors, but I'd be glad to provide those for the record, if you wish.

Mr. PORTER. Which agency is taking the lead on educational efforts to follow up on the conference's recommendations on calcium?

Dr. LOCKSHIN. I can't say that we have specific plans for following up on that. We will of course be looking at what happens after the results of the conference have been published for some time. We have a number of our investigators who recommend calcium supplements to people throughout the country. I don't have a plan for you but. I will provide one for the record.

[The information follows:]

PUBLIC EDUCATION EFFORTS—CALCIUM CONSENSUS DEVELOPMENT CONFERENCE

The results of the consensus development conference on Optimal Calcium Intake, released in June 1994, already have spurred several activities. In the private sector, there has been significant newspaper and magazine coverage of the results of the conference. There is already a great deal of public information related to calcium developed by the dairy industry, by food manufacturers that fortify foods, and by companies that produce calcium supplements. Information from the conference is being used and promoted by private voluntary organizations like the National Osteoporosis Foundation and the Older Women's League.

The NIAMS has two information efforts as follow up to the calcium conference. One is through our newly funded Osteoporosis and Related Bone Diseases National Resource Center. The Resource Center has developed materials that include information from the calcium conference for distribution to the pubic, patients, and health professionals. For the other information effort, NIAMS is working with the NIH Office of Medical Applications of Research, which co-sponsored the original conference, to develop physician education materials out of the conference results, including a test and a slide presentation, which would result in continuing education credits for participants.

The calcium conference has had other significant impact as well. In terms of public policy, the Food and Nutrition Board of the Institute of Medicine, which previously has directed the process of developing nutrition guidelines, has announced its intent to review the calcium intake guidelines and consider the impact of this nutrient on chronic diseases such as osteoporosis.

The calcium conference results are fostering and influencing research. For example, the NIH Women's Health Initiative will be testing the efficacy of calcium supplements in preventing osteoporotic fractures. The women in the trial will be encouraged to eat a calcium-rich diet and be made aware of both the existing Recommended Dietary Allowances (RDAs) for calcium and the conference results.

The NIAMS is particularly focused on following up the research gaps that must be addressed before a new government policy on optimal calcium intakes can be derived. In particular, the calcium intake of adolescent females is far below the current RDAs. We have several projects underway to address the calcium requirements of adolescents and young adults. After the conference, NIAMS initiated a project to determine the effect of calcium supplementation on bone mass in young women between the ages of 20 and 30. The data presented at the conference were not direct, but indicated that bone growth is still occurring during this period. An intervention trial conducted in Nebraska will attempt to confirm this finding. Filling the research gaps through these and other studies will help to strengthen the message to young people to take advantage of the arly years to put bone in the "bone bank" to protect against later antural withdrawals.

NOVEL THERAPIES FOR RHEUMATIC DISEASES

Mr. PORTER. Your testimony mentions a surge of novel therapies developed by the private sector for rheumatic diseases. Could you highlight some of these therapies for us, and tell us why the private sector has taken the lead? Does the market potential for these drugs exceed others because of the high number of people afflicted?

Dr. LOCKSHIN. I think the statement, the private sector has taken the lead, doesn't quite describe the entire picture. There are two treatments that have been prominent in the news recently. One is a treatment that's referred to as anti-TNF alpha. You may not want to know the details of what that term means. That treatment was initially developed after a considerable amount of basic research, not only in rheumatoid arthritis but in immunity and inflammation in general, by grantees of the NIH.

But it was developed into a specific product that could take advantage of those findings by a private company which then tested it, actually not in this country, but in England, and came up with rather startlingly promising results. That company which tested it is an American company from Philadelphia. Having achieved the results that it did in England, it is now bringing that forward to test in the United States to bring it up to potential FDA approval. So they took the final product that had come from a long line of basic research started by NIH.

Another treatment for rheumatoid arthritis that made news last year is oral collagen. A popular way of referring to this treatment is eating chicken bones, but it is somewhat more complex than that. This treatment also developed out of a long history of basic research through NIAMS-funded investigators, and then was taken on by a company to try to make a product out of it. We're not really in the business of making the products so much as we are in the business of creating the basic research that leads up to the products.

ANTIBIOTICS TO TREAT RHEUMATOID ARTHRITIS

Mr. PORTER. Can you tell me what the status is of research on the use of antibiotics long-term to treat rheumatoid arthritis?

Dr. LOCKSHIN. There are three things I can tell you about that. One is that the oral antibiotic trial that was discussed at previous meetings here by Dr. Shulman was completed and was published within the past year. That particular trial showed that a specific oral antibiotic, minocycline, given over a long period of time to patients with rheumatoid arthritis, improved the outcome or improved their status considerably in about 50 percent of the cases.

Mr. PORTER. How long a term was that?

Dr. LOCKSHIN. That was 48 weeks.

Mr. PORTER. Forty-eight weeks?

Dr. LOCKSHIN. Yes, weeks. The good news is that about half the patients responded dramatically to the oral antibiotic. The bad news is that about 40 percent of the placebo group, that is, the control group, also responded. So overall, the difference between the placebo and the trial groups was relatively small.

The second part of the answer concerns an intravenous antibiotic trial, which we were requested to do by the Senate. We have two such trials currently ongoing, one funded extramurally and one funded intramurally. Both of those have just started, thus, there are no results to report.

Third, there are studies, not so much on rheumatoid arthritis but on the destruction of joints, that involve another antibiotic, which presumably is not acting by its antibiotic activity, but acting by a different mechanism that may prevent joint destruction.

Mr. PORTER. How long is the intravenous trial to last?

Dr. LOCKSHIN. The two different intravenous trials, have separate protocols. The one intramurally is, I believe, two weeks. The extramural one is approximately a month of intravenous antibiotics.

Mr. PORTER. There was some thought that 48 weeks was substantially too short a time to make a proper testing of the effect. Have thoughts been forthcoming on holding a longer trial like two to three years?

Dr. LOCKSHIN. No, sir. One of the problems with that is that there is in fact very little substantiated evidence that continuing treatment will be beneficial. If we have the scientific support to suggest that this would be worthwhile, we would be delighted to do that sort of trial. But at the moment, we don't have that type of evidence. Again, speaking as a physician, I am not comfortable continuing to prescribe antibiotics over very long periods of time without evidence that it's beneficial or proof that it is not harmful.

REPETITIVE MOTION INJURY

Mr. PORTER. I'm not a scientist and I don't mean to tell you, I'm simply asking questions because I've heard that that might have some potential.

The Occupational Safety and Health Administration has been developing ergonomic standards for repetitive motion injury. Have you been involved in providing OSHA with any scientific assistance in the development of these standards?

Dr. LOCKSHIN. Yes, in fact, we've done it in a slightly different way than your question implies. Last June, we held a workshop on the repetitive motion syndrome; a book is about to be published detailing the results of that. This workshop is a conference of national experts that we convened to examine all the phases of repetitive motion syndrome such as ergonomics, looking at the anatomy of the structures involved, and looking at some of the basic molecular biology of tendons and other structures.

At that conference, participants from OSHA were prominent participants. In addition, the final document is being written by someone from OSHA. We are working closely with them, but not precisely in the way that you suggested.

GENE THERAPY TO TREAT SKIN DISEASES

Mr. PORTER. Your budget justification mentions the use of skin to treat diseases of other organ systems through sustained release of drugs through a gene gun technique in which skin cells act as carriers for human genes. What diseases might be most amenable to this type of treatment?

Dr. LOCKSHIN. That isn't as easy to answer as it sounds. The skin is an organ that has the capability of transmitting large numbers of things to the general body. And virtually any type of gene that one might want to insert could be inserted through the skin.

Among things that we could look at, for instance, would be diseases like muscular dystrophy. But it will depend on the very technical components of whether the gene being looked at is small enough to get through the skin in an undamaged form. There are a number of technical questions that would specifically depend on that. Obviously all the skin diseases that we're looking at could be treated that way.

DISEASE REGISTRIES

Mr. PORTER. I'll ask one more question before I yield to Mr.

ers to establish disease registries. Is this because of the sheer number of diseases under your jurisdiction or because many of them are in the early stages of scientific investigation?

Dr. LOCKSHIN. Both of those answers are correct. Also, these diseases are often tremendously devastating and create tremendous anxiety in the persons afflicted with them. In addition to that, they often are very good models for other diseases, and the information we get from studying one disease often is applicable to many.

For instance, we have had registries for many years now on the disease epidermolysis bullosa. From that initial registry, we learned virtually how the skin is put together, molecule by molecule, what makes it hold together and so on. This has been applicable now to a whole variety of other skin diseases. The registries that we just funded within the past year include a registry on scleroderma. This is not only a terrible disease, but one that can give us a model of things like scarring, for instance, and how the skin responds to injury.

We have a registry for ichthyosis, it's another one of the congenital diseases. We have one for juvenile dermatomyositis, a quite rare disease, but one that tells us a great deal about how children grow, what happens to their muscles and so on. We have one on juvenile rheumatoid arthritis, which is clearly a disease of concern to many people. The last registry is on the relatively rare disease called neonatal lupus, which is transmitted from mother to child and tells us about how mothers carry children, how children's hearts are formed and all sorts of things. So there's a good deal more to the registry than just the fact that it's a registry.

Mr. PORTER. But you're expanding the number of registries that you have?

Dr. LOCKSHIN. At the moment, we just expanded, we added five in the past year, we don't have plans to expand again for another couple of years.

Mr. PORTER. We also hear from groups that are interested in establishing tissue banks for various diseases. How would you compare the usefulness of tissue banks to registries?

Dr. LOCKSHIN. Registries can be defined in a number of ways. They could include tissue banks. The registries that we just funded are more narrowly defined. They're collections of patients and patient data, and in some cases we have the ability to get blood samples or tissues from biopsies. The differences are largely those of expense and the ability of investigators to use the tissues and those sorts of things.

But the eventual outcome of registries, in addition to being sources for potential treatment trials, will be sources for tissue banks. These will probably be funded separately.

Mr. PORTER. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Good afternoon, Dr. Lockshin.

Dr. LOCKSHIN. Good afternoon, Mr. Stokes.

CLINICAL TRAILS

Mr. STOKES. Doctor, what major clinical trials on arthritis are underway?

Dr. LOCKSHIN. Perhaps the easiest way to start is to say that we have many different types of arthritis. Trials that we're currently doing intramurally include trials on kidney disease in lupus, which is a type of arthritis, and trials on severe rheumatic diseases, and that includes both rheumatoid arthritis and the arthritis that is associated with psoriasis, known therefore as psoriatic arthritis. We have had trials on preventing skin cancers in certain types of rare skin diseases that make people prone to that.

In addition, we fund trials extramurally. Just before you walked in, we had mentioned the intravenous antibiotic trials, and we have had trials on a variety of biological agents, that's the new type of drugs in rheumatoid arthritis. We have trials also on osteoporosis and our other diseases as well.

ARTHRITIS IN CHILDREN

Mr. STOKES. You mentioned arthritis in children. How extensive a problem is that?

Dr. LOCKSHIN. I'll give you precise numbers if I can. Approximately 200,000 children in the United States have rheumatic disease. Of those, approximately 71,000 have the disease that we know of as juvenile rheumatoid arthritis. When I speak of arthritis in general, that includes dermatomyositis, the one for which we just funded a registry. Arthritis also includes lupus and a whole host of other diseases.

Mr. STOKES. Do you collaborate at all with the Child Health Institute regarding this area of research?

Dr. LOCKSHIN. On juvenile arthritis, we have several collaborations with the National Institute of Child Health and Human Development. On juvenile arthritis, and particularly on a bone disease that's known as osteogenesis imperfecta, we have collaborations on the rehabilitation of children affected with that. In addition, there is another collaboration that has to do with the outcomes of pregnancies in some patients.

OSTEOARTHRITIS

Mr. STOKES. I noticed in your opening statement you indicate that osteoarthritis is the most common of all the rheumatic diseases, affecting an estimated 16 million Americans. It costs the Nation an estimated $8 billion each year. It further indicates that this disease is a major reason for artificial hip joint replacements. Prevention and controlling the frequency of this problem are key. Tell us what major research initiatives are underway to address this health problem with respect to diet and nutrition and exercise? Are we making any progress?

Dr. LOCKSHIN. First I'll tell you about the initiatives that we've done. Last spring we had a national conference on osteoarthritis, the results of which will soon be published. We asked the experts for their best ideas, and based on their advice and with our own thinking we issued a request for applications for basic science in osteoarthritis. We've received 72 applications, and approximately 6 to 8 of those will be funded this summer.

As yet, I have not been able to look at the 72 applications, and I don't know how many deal with diet or exercise, both as a cause and as a repair of osteoarthritis. It is always a topic that is of high interest to the Institute. I'm talking about the athletes who develop arthritis on the one side, as well as the activities, particularly in older people, that keep them from becoming disabled by arthritis on the other. I think I've answered your questions. Did I miss a part of it?

LUPUS

Mr. STOKES. I think you've covered most of it, Doctor.

You mentioned earlier lupus. Over the past several years, your Institute in particular has played a major role promoting research on lupus. And as you know, African American females suffer a disproportionately higher rate of lupus than the general population. What is the extent of lupus in the American population, and in particular, African American women? And also tell us, what is the estimated cost to the nation annually?

Dr. LOCKSHIN. In terms of the frequency of lupus in the nation, we estimate that there are just under 200,000 cases nationally. Although there have been some recent estimates that suggest a higher number, we haven't been able to confirm them at the present time. African American women are affected about three times as frequently as are white women, and some people believe that they are affected more seriously.

I don't have a number for you on the cost of the illness. There have been some very crude estimates, but we've chosen to give you only numbers that we're relatively comfortable with. For that reason, I can't speak specifically to that. I'm sorry, was there another part of the question?

Mr. STOKES. No, I do have another part to that question.

What I'd like to know in terms of this particular diseases is, what progress have we made since you were here last year? Have you made any progress?

Dr. LOCKSHIN. Yes, we have. Last year at these hearings we were just aware of the important finding that a gene was responsible for the disease in a certain type of mouse. There have been several people now looking at this in humans, and the results are somewhat conflicting. Some investigators believe that this is in fact a critical gene in humans and others do not.

Very recently a grantee of ours in Oklahoma published a paper indicating that a very small part of a protein called a peptide could create the disease in animals. This peptide consists of eight amino acids. With that little eight-unit part of a protein, the investigator could create the disease in animals. This to me is an extraordinarily exciting event, because it means that we could zero in on the exact cause of the disease.

We are also looking intensively, based on a study that we funded two years ago, at the differences between African Americans and whites with lupus. We're starting to see papers that are looking closely at what that means. Some investigators are examing the genetic side, and we have some plans in the very near future to mount an intense effort to find the genes for lupus. That's the one side of the picture.

The other is trying to uncouple the link between socioeconomic status and race in the country, and that is a harder thing to define. We have a chance, however, of sorting that out probably within the next few years.

Mr. STOKES. What portion of your budget, Doctor, is being applied to research on this particular disease?

Dr. LOCKSHIN. We estimate funding for lupus in fiscal year 1995 will be $19,600,000. The amount for fiscal year 1994 was approximately $19,000,000. In 1996, we estimate $20,200,000.

Mr. STOKES. Okay, you are projecting a slight increase.

Dr. LOCKSHIN. That's correct.

SKIN ULCERS

Mr. STOKES. Let me ask you, the skin ulcers which fail to heal are of major concern to the elderly, particularly patients who are bedridden, in hospitals, nursing homes, quadraplegics and the diabetic patients with diabetic ulcers. I understand the cost of healing one bed sore for one patient may be as much as $40,000. What research is underway to relieve this type of suffering and effectively treat skin ulcers and wounds that fail to heal?

Dr. LOCKSHIN. We again called a group of experts together to discuss this problem in January 1993. We conducted a very thorough evaluation from as many points of view as possible. On the basis of these recommendations, we issued a request for applications, and we funded several awards. We were supported in this effort by other Institutes, such as the National Institute of General Medical Sciences. We now have work being done, that is looking at the ability of the wound to clot, the ability of blood vessels to get into the wound and the number of chemicals that both create inflammation and reduce inflammation in the wounds. We have additional research being conducted on artificial skins.

In January of 1995, we followed up, as we had planned to do, with a program announcement to encourage even more research in this field. This effort was supported by not only our Institute, but also the Aging Institute, Child Health and Human Development, General Medical Sciences, and Nursing Research. We believe that we're going to make a good deal of progress in this area based on thse efforts.

Mr. STOKES. Thank you, Dr. Lockshin.

Thank you, Mr. Chairman.

LOW BACK PAIN

Mr. PORTER. Thank you, Mr. Stokes.

Earlier we had the Agency for Health Care Policy and Research before us. And I believe they mentioned back pain as among the top three in terms of cost to society. I think their cost figure was $20 billion, perhaps. And they had done a study on back pain. Did you have anything to do with their work on that?

Dr. LOCKSHIN. They issued guidelines on low back pain, and while we did not officially participate in that, a number of our investigators and staff members provided advice.

Mr. PORTER. So would you say that your research agrees generally with what the recommendations were of the Agency?

Dr. LOCKSHIN. I would again put on my doctor hat and say I do agree. From the Institute's point of view, we have no reason to disagree with the specific recommendations that were made.

I would say that we are concerned about the problem of back pain. As you indicate and as I indicated in my opening statement, this is a major problem for the country. In November of 1995, we're again convening a group of experts to look at the problem. We're doing this in a somewhat imaginative way, or a different way than we've done it before, because we've not gotten the types of results that we would like. Actually, I would congratulate Dr. Stephen Gordon, the director of our musculoskeletal diseases branch, for devising this.

This conference in November will look at three separate problems from the point of view of what causes the pain. These are back pain without any nerve involvement, back pain with sciatica, and the disease common to older people, spinal stenosis, where the outgrowths on the bone in the spine crush the spinal nerves.

We hope by using this somewhat different approach we will get a better idea of innovative ways to look at the problem that will be more successful than in the past. Following this workshop, we will analyze the ideas that we hear and then consider the best options, such as a request for applications.

Mr. PORTER. We understand that the orthopaedic surgeons were very upset with the recommendations of the Agency for Health Care Policy and Research because the suggestions were that a good deal of back surgery is either unnecessary or ineffectual. I note that the American Academy of Orthopaedic Surgeons is the cosponsor of your conference in November and wonder if there's any connection.

Dr. LOCKSHIN. No, the recommendation had nothing to do with the conference. I would say that one of the reasons for the concern or the outcry about the health care policy research guidelines was a misunderstanding. Those guidelines were for acute back pain. There's a difference between acute back pain, which was the focus of the recommendations, and recurrent back pain with nerve injury, which might lead to surgery.

A simplistic reading of the guidelines might indicate you shouldn't be doing surgery. But in fact if you look at the qualifications that are in the guidelines, you understand that there are some cases when in fact you should be doing surgery, and others when you should not. The guidelines were for uncomplicated acute back pain.

Mr. PORTER. Well, you wouldn't do surgery for a non-chronic problem anyway, would you?

Dr. LOCKSHIN. No, probably not. But, again, there are circumstances that could lend themselves to surgery. If you take out complications like tumors and other sorts of things, the answer is no for acute back pain.

GENETIC LINKS TO LUPUS

Mr. PORTER. You're increasing your research in the areas of genetic links to lupus. Do you think genes are likely to be associated with susceptibility, or that they actually will be found to be a cause of the disease?

Dr. LOCKSHIN. I believe that this is very likely. As you know, there are a number of mouse models of lupus, and in the past year there have been publications that have focused on the genetic controls of lupus in mice. One of our investigators in California identified a group of eight genes which, depending on the pattern in which they occurred in these mice, dictated the type of lupus that the mice contracted, an extraordinarily powerful finding.

We believe that a similar approach will be important in humans. We have access now to a very large collection of families of patients with lupus, and we expect that we will be able to use these families to look for the gene. My guess is that we will find not one gene, but several genes that determine the disease.

FIBROMYALGIA

Mr. PORTER. The disease fibromyalgia has been brought to the subcommittee's attention over the last few years. Is the state of science regarding this disease adequately advanced to justify further increasing the level of effort in research?

Dr. LOCKSHIN. The easiest way to answer that is that we again convened experts to discuss the problem in May 1993. The Institute determined that the best approach was to look for hard science that could be applied to this particular field. As a result we issued a request for applications in 1994 from which we funded five awards. These grants all examine very basic aspects of fibromyalgia. Some grants look at the way in which the brain controls both inflammation and pain.

Another looks at the interaction between Lyme disease and fibromyalgia. We expect that these types of research projects will help us gain a real handle on fibromyalgia that we can use to develop both more research and, potentially, more directed therapies than we have right now.

INHERITED DISORDERS OF CONNECTIVE TISSUE

Mr. PORTER. Do you plan on an initiative to accelerate research into inherited disorders of connective tissue? Is a common approach likely to be effective for these varied diseases, or do you have to attack each one by one?

Dr. LOCKSHIN. The answer is both of those. The diseases tend to have common links. As I mentioned earlier, in our registries for epidermolysis bullosa we found clues that led us to a wide variety of inherited skin diseases. Similarly, in the disease Marfan syndrome, an abnormality of a protein called fibrillin has been identified. As researchers look further at that protein, they find other abnormalities that are relevant to similar types of diseases, as well as information about how the skeleton is constructed.

An intramural project is focusing on a disease not commonly seen in the United States called familial Mediterranean fever. This particular disease may be the model for all inflammation for all the rheumatic diseases. The NIAMS investigator, Dr. Kastner, is close to finding the gene for this disease. Again, we expect the answer will be much more generalizable once we have it.

Mr. PORTER. Mr. Stokes, any additional questions?

ROLE OF EXERCISE IN HEALTH

Doctor, as we watch children in our nation today, we see them spending more and more time watching TV, playing video games and other things of the sort. As the lack of exercise and the associated costs to the Nation in physical, social and economic terms is devastating, what outreach is underway to make the public aware of the long-term health problems that can result from this type of behavior, and to prevent or perhaps at least postpone any adverse impact?

Dr. LOCKSHIN. We do have a number of efforts dedicated to the role of exercise in health. I think that was the direction of your question. These efforts focus on the older population rather than the younger population, but it works for both. We have trials and recommendations about exercise for building both muscles and bones. We have a particular interest in helping young girls build bones through exercises. We are also studying the weaknesses that occur in both muscles and bones in people who are bedridden and in people who go up in space.

In terms of educating the community, we've recently funded a resource center on osteoporosis and other diseases. The important point is the relation between bone strength and exercise. The NIAMS also has its own communications office that disseminates information about exercise and about general healthy living to the country at large.

DISPARITIES IN HEALTH CARE

Mr. STOKES. Over the past several weeks, we've had a great deal of testimony from various witnesses who have talked to us about the disparities in health care between minorities and the majority population. And, you talked earlier about lupus, and how much more seriously it affects African American women.

With respect to your Institute, are there other areas where we find this type of disparity in minority health, and are you doing any special type of research in terms of minorities, besides lupus?

Dr. LOCKSHIN. Yes, we do. One of the things that's come up deals with osteoarthritis. We have learned that total knee replacements in patients with osteoarthritis are much more frequent in white Americans than in African Americans. The reasons for this are not clear, and we have projects that are trying to determine that. Among the reasons might be the way in which patients are perceived by their doctors or the way the patients think of and trust their doctors.

One of the things that's rather unique about our Institute is the way things happen through our research centers program. These centers look at a variety of diseases such as lupus, ankylosing spondylitis, rheumatoid arthritis, and osteoporosis.

Our center investigators have added minorities to their investigative teams, in some cases Native Americans, in some cases African Americans, in some cases Hispanics, in an attempt to reach out to communities and to encourage their participation in our studies.

Getting people to respond and willingly participate with the same degree of trust from one study to the next is a difficult problem.

With this approach we hope to not only find out about the health of individual populations, but also to find out why people don't participate or do participate in these studies.

Mr. STOKES. Do you get good cooperation from the community or from community organizations when you reach out?

Dr. LOCKSHIN. The information we have received has been very, very positive. For instance, while the Women's Health Initiative is not our Institute's activity, we have specific involvement in the 10 centers that focus on minority participants. The addition of centers specifically dedicated to recruiting minority persons as well as adding representatives from minotiry populations to the recruitment teams, has made a world of difference.

I don't think there's any question at all that this has been helpful.

Mr. STOKES. Thank you very much, Dr. Lockshin.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Lockshin, those are all the questions. We very much appreciate your coming to testify today. You did an excellent job, and we will take your budget under advisement.

Dr. LOCKSHIN. Thank you, it's my pleasure.

[The following questions were submitted to be answered for the record:]

FUNDING FOR DISEASES

Mr. Porter: Identify 1994-1996 spending for the following diseases: osteoporosis, rheumatoid arthritis, osteoarthritis, lupus, Lyme disease, epidermolysis bullosa, ichthyosis, psoriasis, alopecia, scleroderma, osteogenesis imperfecta, Marfan's syndrome, and fibromyalgia.

Dr. Lockshin: Funding for these diseases in fiscal years 1994 through FY 1996 is as follows:

	FY 1994 Actual	FY 1995 Estimate	FY 1996 Estimate
Osteoporosis	$43,836,000	$45,500,000	$46,900,000
Rheumatoid Arthritis	17,022,000	17,610,000	18,210,000
Osteoarthritis	14,395,000	14,920,000	15,400,000
Lupus	18,967,000	19,600,000	20,200,000
Lyme disease	3,807,000	3,950,000	4,070,000
Epidermolysis bullosa	7,193,000	7,600,000	7,820,000
Ichthyosis	4,555,000	4,750,000	4,890,000
Psoriasis	2,486,000	2,600,000	2,700,000
Alopecia	387,000	400,000	410,000
Scleroderma	2,789,000	2,880,000	2,970,000
Osteogenesis imperfecta	1,407,000	1,460,000	1,500,000
Marfan's syndrome	1,303,000	1,350,000	1,400,000
Fibromyalgia	1,431,000	1,480,000	1,530,000

RESEARCH CENTERS

Mr. Porter: Identify the number, type and subject matter of the research centers supported in 1995.

Dr. Lockshin: The NIAMS will support 30 research centers in FY 1995. These include 14 Multipurpose Arthritis and Musculoskeletal Diseases Centers (MACs), 9 Specialized Centers for Research (SCORs), 6 Skin Disease Research Core Centers (CORE), and 1 Juvenile Rheumatic Diseases Research Center Planning Grant. Included in the nine SCORs are 4 in rheumatoid arthritis, 2 in osteoporosis, 2 in systemic lupus erythematosus (SLE), and 1 in osteoarthritis.

OSTEOPOROSIS

Mr. Obey: Osteoporosis and related bone diseases destroy the quality of life and require care over long periods of time. By the year 2020, when the baby boom generation approaches the prime years for the onset of chronic illnesses, a large percentage of the population could be afflicted with osteoporosis and related bone diseases. Please tell me what plans you have to increase research efforts for osteoporosis and related bone diseases.

Dr. Lockshin: The Institute is keenly aware of the projected growth of the population aged 65 years and above over the next 25 years. In an effort to blunt the anticipated increase in osteoporosis and related bone diseases, the Institute has the following plans:

(1) As a result of a request for applications issued last year, the Institute will soon fund new research on promising cellular, molecular, and genetic approaches to osteoporosis. Such research could translate into more effective ways to prevent and repair weak bones. NIAMS is the lead Institute on this initiative to which NIA and NIDDK have also committed funding.

(2) In June 1994 NIAMS convened a panel of experts to evaluate data on optimal levels of calcium intake. The panel made specific recommendations for the amount of calcium that should be consumed daily by each segment of the population, including children, young adults, men, and both pre- and post-menopausal women. The Institute initiated a clinical trial in which young women are taking calcium supplements to determine whether this helps build stronger bones. Additionally, the Institute is planning to disseminate information to the public dealing with calcium nutrition.

(3) In September 1994, the Institute established the National Resource Center on Osteoporosis and Related Bone Diseases. The National Resource Center will provide state-of-the-art information on how best to prevent bone diseases (proper diet, exercise, etc.) and fractures (avoiding high-risk situations, falling "the right way," etc.).

(4) The Institute recently established an osteoporosis data group whose goal is to assemble accurate prevalence and incidence data.

(5) NIAMS is working with the Veterans Administration on plans for a study of osteoporosis in men.

Mr. Obey: Although 20 million of the 25 million Americans who suffer from osteoporosis are women, critical research on both military men and women is sorely necessary. Last year, Congress appropriated $5 million under the Defense Research and Engineering Office to conduct research in cooperation with NIAMS. Please tell me how NIAMS and the Department of Defense have worked together on this and specifically what each department's role is in this cooperative effort.

Dr. Lockshin: The Institute has learned that the Department of Defense (DoD) does not consider osteoporosis research to be a high priority in addressing the medical needs of U.S. operational forces. DoD is currently evaluating its earmarked funds to determine the most cost-effective investment strategy compatible with its commitment to battlefield preventive medicine and combat casualty care. NIAMS continues to be eager to coordinate research efforts with all organizations having an interest in osteoporosis.

LOW BACK PAIN

Mr. Bonilla: It has been reported that low back pain and spine injuries represent the overwhelmingly largest cost factor in workers compensation cases--placing a significant burden on business. We understand that your Institute will sponsor a workshop this fall on low back pain. What do you hope to achieve?

Dr. Lockshin: In collaboration with the American Academy of Orthopaedic Surgeons, NIAMS is organizing a workshop entitled "New Horizons in Low Back Pain" to be held November 1-4, 1995. The workshop will focus on three clinical issues: isolated low back pain, low back pain with pinched nerves, and narrowing of the spine. The Institute hopes to stimulate further research on this huge public health problem.

Mr. Bonilla: Will you focus on the prevention of low back pain, which is clearly a major component of the solution to this universal health problem and should result in some cost-savings?

Dr. Lockshin: A major concern of the workshop will be not only diagnosis and treatment of the three clinical issues, but also development of interventions that could reduce future public health expenditures.

Mr. Bonilla: How will you promote further research on this important public health problem that affects between 60 to 80 percent of the population?

Dr. Lockshin: Following the workshop, NIAMS will actively pursue additional research on low back pain. Publication of a book of manuscripts and workshop discussions should serve as a further stimulus to research in this area.

REPETITIVE MOTION DISORDERS

Mr. Bonilla: According to the Bureau of Labor Statistics the occurrence of repetitive motion disorders in the workplace is increasing in alarming numbers. And these conditions of the active employed account for an increasingly large proportion of workers compensation costs and for other costs such as those related to lost work days. We also understand that major lawsuits have been brought against industry because of these injuries. What steps has NIAMS undertaken to better understand the cause of these potentially crippling disorders, to improve the diagnosis and treatment, and to define preventive measures?

Dr. Lockshin: Recognizing the magnitude of the problem, NIAMS assembled a team of nationally recognized researchers on repetitive motion disorders in June 1994. Manuscripts and discussion summaries will be published as a book this spring. This unique presentation of basic and clinical science is expected to stimulate further investigations that will lead to improved diagnosis and treatment, as well as preventive measures.

POTENTIAL FOR OVERLAPPING RESEARCH

Mr. Dickey: In what ways might your research at NIAMS overlap with research done at the National Institute on Aging (NIA)?

Dr. Lockshin: Although it might appear that there is overlap, NIA focuses on problems as they relate to aging, while NIAMS focuses on normal organ system biology and on disease pathogenesis. Thus NIA would look at osteoporosis and osteoarthritis as a general phenomenon of how the body ages and as a result of multiple organ system frailty in the elderly, while NIAMS studies general disease progression, injury, repair, and treatment in cartilage and bone.

Mr. Dickey: How do you assure that the overlap is minimal?

Dr. Lockshin: NIAMS interacts very closely with NIA to ensure that no research is duplicative. For example, there is an early-warning system with respect to issuance of requests for applications to keep each institute apprised of the other's research initiatives.

Where there is potential for overlap, NIAMS and NIA share responsibility. In a dually issued RFA, for instance, each institute would accept assignment for applications according to the criteria listed above, with ambiguous assignments negotiated between the institutes.

HIP REPLACEMENTS

Mr. Dickey: What recent advancements have been made regarding hip replacements?

Dr. Lockshin: Over the years, both private sector investigators and NIH-funded researchers have done much to improve on the original total hip replacements (THRs) of the 1960s. The first major effort to study the bone remodeling response to various biomaterials was supported by the NIH. Research on thickness and shape requirements for polyethylene cups and basic studies on control of bacterial infections as a sequel to joint surgery were also supported by the NIH. After many years of use THRs often fail. A recent grant to a small, private-sector firm resulted in development of an ion implantation process applied to the surface of titanium balls (the articulating part of the prosthesis) to produce less friction and wear than unmodified titanium balls. This and other innovations have already been applied to several hundred thousand devices, and early retrievals show superior wear resistance. With the results of currently supported and future research, it is now possible to envision joint replacements that will last for 20 years or more.

Mr. Dickey: What is the rate of successful hip replacements, allowing the patient reasonable mobility after the replacement:

Dr. Lockshin: More than 120,000 artificial hip joints are implanted annually in the United States. The successful replacement of deteriorated hips permits nearly all patients (greater than 95%) to resume comfortable independent living. Ninety to 93 percent of all THRs are never revised.

REPETITIVE MOTION DISORDERS

Mr. Dickey: What research is conducted at NIAMS in the area of repetitive motion injuries?

Dr. Lockshin: Recognizing the magnitude of the problem, NIAMS assembled a team of nationally recognized researchers on repetitive motion injuries in June 1994. Manuscripts and discussion summaries will be published as a book this spring. This unique presentation of basic and clinical science is expected to stimulate further investigations that will lead to improved diagnosis and treatment, as well as preventive measures.

SKIN DISEASES

Mr. Stokes: Skin ulcers which fail to heal are a major concern to the elderly, particularly patients who are bed-ridden in hospitals, nursing homes, quadriplegic, and for diabetic patients with diabetic ulcers. I understand the cost of healing one bedsore for one patient may be as much as $40,000. What research is underway to relieve this suffering and effectively treat skin ulcers and wounds that fail to heal?

Dr. Lockshin: Scientists are making significant progress in describing how wounded tissue heals. They have identified a number of growth factors, specialized molecules that exert their actions during different stages of wound healing, and are exploring their use in the treatment of a wide variety of wounds. In January (1995) NIAMS issued a program announcement to further enhance research in this area. Grant applications are expected dealing with molecules that influence inflammation, the migration of cells to form new skin, and the role of oxygen depletion at the wound site.

EPIDERMOLYSIS BULLOSA

Mr. Stokes: Having found the abnormal genes that cause EB, how is this knowledge being used to further research advances in this area?

Dr. Lockshin: Now that the defective genes and abnormal proteins in some forms of EB have been found, there is potential for early (including prenatal) diagnosis and gene therapy. NIAMS expects to see the first attempts at gene therapy in the near future. The most likely candidate illness is recessive dystrophic EB.

NEUROSCIENCES RESEARCH

Mr. Stokes: Last month, the committee had the opportunity to hear testimony from the Nation's Nobel laureates. We welcomed the insight they provided on the status of the Nation's biomedical research enterprise. They indicated that neurological research was one of the most important areas that--if enhanced--offered considerable opportunity to further medical advances. To what extent is this area of research a high priority for your institute?

Dr. Lockshin: Neurology-related research is being pursued with respect to several diseases under the Institute's mandate. In June 1994, NIAMS sponsored a conference on the neurologic control of pain in rheumatoid arthritis and osteoarthritis. Experts developed an agenda for areas in need of additional research. Currently, extramural investigators are investigating the central nervous system involvement in lupus and the neurologic manifestations of Lyme disease. NIAMS intramural scientists are studying the role of the neuroendocrine system in the development of arthritis and fibromyalgia.

NIAMS is the lead institute at the NIH for research on fibromyalgia, a chronic disorder characterized by pain and stiffness throughout the tissues that support and move the bones and joints. The cause of the disease is unknown, but some scientists believe that it occurs as a result of an injury or trauma that profoundly affects the central nervous system. Some of the grants that the Institute recently funded to enhance research on fibromyalgia deal with altered activity of specific brain structures and how these alterations might be the source of pain.

Mr. Stokes: How much is included in your FY 1996 budget request for neurological research? How does the FY 1996 funding estimate compare with 1995 and 1994?

Dr. Lockshin: Funding for neurosciences research for FY 1996 is estimated at $2,170,000 compared to an estimate of $2,110,000 in FY 1995 and actual obligations of $2,035,000 in FY 1994.

MINORITY HEALTH

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health, in testimony before the committee this year, indicated that the Department is enhancing its efforts to close the health disparity gap. While this issue is complex and a multiplicity of factors contribute to the disparity including life style and access to health care, biomedical research does have a key role to play in helping to close the gap. What are the most significant activities underway at the Institute to help address this national problem, and in terms of progress, what can you tell us this year that you could not tell us last year?

Dr. Lockshin: The most significant minority health activities underway at the Institute involve lupus, arthritis of the spine, and osteoporosis. In the area of lupus, the Institute started a public education campaign in 1991 and expanded it in 1994. In 1993, NIAMS issued a request for applications for research on lupus in women and minorities, and grantees are beginning to publish results on differences in lupus in whites and African Americans.

Another area in which the Institute is conducting research on minority health is arthritis of the spine. Indigenous people of Alaska have a genetic predisposition to arthritis of the spine. NIAMS is attempting to learn more about the cause and course of this disease. NIAMS is also examining an excess of rheumatoid arthritis among Pima Indians.

The Women's Health Initiative, which seeks to address the preventive aspects of cardiovascular disease, cancer, and osteoporosis, was initiated in 1992. Two aspects of the clinical trial--estrogen therapy and diet supplementation--pertain to prevention of osteoporotic fractures. In 1993, 16 vanguard clinical centers were established, and an additional 24 clinics were set up in September 1994. They began recruitment in February 1995. Ten of these 40 clinical centers focus on minority populations. The center in Arizona focuses on recruitment of Hispanics and Native Americans; the one in Georgia, on African Americans. The Chief of the NIAMS Bone

Biology and Bone Diseases Branch is serving as project officer for the Arizona center.

Mr. Stokes: Please describe your Institute's efforts to ensure that the particular concerns of minorities and women have not been overlooked in research, research training, and outreach funded by the Institute.

Dr. Lockshin: Under the Institute's mandate are many diseases that affect minorities and women disproportionately. Those that occur to a greater extent in minority populations than in the majority of Americans include lupus and rheumatoid arthritis. The former disproportionately affects African Americans; the latter, Pima Indians. Diseases that have higher frequencies in women than in men include osteoporosis, lupus, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and fibromyalgia. Since the beginning of FY 1993, the Institute has sponsored or cosponsored 12 research initiatives directed towards enhancing the health of minorities and women. Also during this time NIAMS established two specialized centers of research devoted to lupus.

In an attempt to enhance minority involvement in research, the Institute has funded about 30 extramural grant supplements annually for training of underrepresented minorities. In addition, NIAMS supports a Minority Travel Award Program and a Minority Investigator Research Enhancement Award. The latter provides support for faculty members of minority institutions to collaborate with principal investigators of active research funded by NIAMS. The Institute will soon convene a meeting of graduates of its minority training programs.

NIAMS also offers summer training opportunities for minority students in its intramural laboratories, and an enrichment program for a nearby high school whose student body is composed primarily of minorities. In addition, the Institute conducts minority recruitment efforts at national conferences. In the spring of 1993, the Institute cosponsored an initiative to promote reentry of investigators--primarily women--into biomedical and behavioral research careers.

The Institute's outreach efforts for minorities and women include developing instruction kits on lupus focusing on African American women, and promoting minority health at its multipurpose arthritis and musculoskeletal diseases centers. The Institute's clearinghouse has produced information in Spanish.

Last fall, the Institute established the National Resource Center on Osteoporosis and Related Bone Diseases. The center will provide state-of-the-art information on the treatment and prevention of bone diseases to health professionals, patients, and the public.

IMPACT OF AIDS RESEARCH ON OTHER DISEASES

Mr. Stokes: To what extent has knowledge gained in your AIDS research effort had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your institute?

Dr. Lockshin: The Institute continues to support research on AIDS as it relates to arthritis and musculoskeletal and skin diseases. A condition known as DILS (diffuse interstitial lymphocytosis syndrome) closely resembles Sjogren's syndrome--a rheumatic, autoimmune disease--in persons who are infected with the AIDS virus. Interestingly, patients with DILS have a lower rate of opportunistic infection than do others who are HIV-positive. Researchers are attempting to discover why the evolution of HIV into highly replicating strains appears to be blunted in patients with DILS. This knowledge could lead to a better understanding of how Sjogren's syndrome and related autoimmune diseases develop.

Skin involvement is a prominent feature of HIV infection. Virtually all patients infected with HIV develop one or more skin diseases during the course of infection. As patients infected with HIV live longer, these conditions can become a major factor in quality of life. Although most of these skin disorders are at least initially treatable by standard dermatologic modalities, they either become resistant to or too severe for such treatments to be effective during later stages of HIV infection. There is anecdotal evidence in the scientific literature for the efficacy of innovative (non-FDA-approved) approaches and/or combination therapies, but little in the way of controlled studies to indicate efficacy, side effects, or cost. The Institute is undertaking an initiative to stimulate clinical studies in skin diseases associated with HIV/AIDS.

OPPORTUNITIES

Mr. Stokes: Please describe the most promising opportunities in basic as well as clinical research in arthritis and lupus that you see for the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Lockshin: Opportunities for advancing knowledge in three major types of arthritis--rheumatoid arthritis (RA), osteoarthritis (OA), and arthritis of the spine--abound. RA is characterized by the development of markedly swollen joint tissue, which results from angiogenesis, the abnormal formation of new blood vessels. NIAMS-supported researchers have recently produced a novel angiogenesis inhibitor that can slow and even prevent the chronic inflammation of arthritis in several animal models. The inhibitor is currently undergoing preliminary clinical trials, and the Institute plans to expand its efforts in this field. Better understanding of angiogenesis, its role in destructive diseases such as RA, and the effects of angiogenesis inhibition could provide effective means to manage a wide range of joint problems.

In a survey covering the period 1965-1985, joint replacement procedures were rated as the leading clinical advance in the management of osteoarthritis. In an effort to further improve care of patients and combat escalating health care costs, the Institute has established a special research initiative in orthopaedic biomaterials that is a multidisciplinary approach combining advances in mechanical science with advances in biology. With the results of currently supported and future research, it is now possible to envision joint replacements that will last for 20 years or more.

In recent years there has been a significant enhancement of basic knowledge about how enzymes break down cartilage and bone in osteoarthritis. NIAMS now intends to direct a multiple mechanism, collaborative effort to develop a broad program of basic science cartilage research, and in a parallel manner to stimulate new research to translate current bone biology research into clinical applications. Success in this initiative will markedly reduce the burden of osteoarthritis.

In a ground-breaking study on the causes of spinal arthritis, researchers have now proven in an animal model of the disease that the presence of an infectious agent and genetic susceptibility are both necessary for the disease to occur. The opportunity exists to identify the responsible infectious agent and develop an intervention that would block the link between the gene and the infectious agent, thereby preventing the arthritis from occurring. Long-term future directions of the Institute include gene and/or antibacterial therapy for arthritis of the spine.

Susceptibility to lupus has been unequivocally established to be an inherited trait. Recently, NIAMS-supported researchers in California analyzed 90 percent of the genome of a strain of specially bred mice that spontaneously develop a lupus-like condition as they mature. The researchers found places on eight different chromosomes to be associated with manifestations of lupus such as abnormal antibodies in the blood, kidney disease, and enlarged spleen. Working collaboratively with the National Center for Human Genome Research, NIAMS is initiating an effort to identify genetic susceptibility in humans. This could pave the way to development of definitive preventive and treatment strategies for lupus.

SUCCESS RATES

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the congressional justification, the NIH's FY 1996 budget would support a success rate of 23 percent. What has been the trend with respect to your institute's success rate?

Dr. Lockshin: The success rates for NIAMS and for NIH overall from FY 1987 through FY 1996 are presented below. As with most Institutes, NIAMS experiences some fluctuations in success rate from year to year depending on commitments for noncompeting awards in any given year. With regard to success rate trends, however, the data reveal (with the exception of FY 1991) that the NIAMS has consistently been significantly below the NIH average. This is true despite the fact that the Institute expends 67 percent of its budget on RPGs--10 percent more than the NIH average--and despite the fact that the Institute maintains one of the most vigorous cost management plans at the NIH.

Fiscal Year	NIAMS Success Rate	NIH Success rate
1987	28.5%	34.9%
1988	26.1%	32.4%
1989	26.4%	27.6%
1990	20.0%	24.0%
1991	31.3%	29.3%
1992	17.5%	29.6%
1993	20.9%	24.5%
1994	19.6%	24.4%
1995*	19.9%	24.0%
1996*	20.9%	23.0%

(*Estimated)

AVERAGE COSTS

Mr. Stokes: What has been the trend in the average cost of research project grants?

Dr. Lockshin: The average annual increase of research project grants, in total, has been 4.6 percent over the 9-year period from 1987 through 1996. Because the NIAMS has a relatively small portfolio of research project grants, annual increases do vary, depending on the particular mix of grants in any given year. The Institute strictly adheres to the guidelines contained in the NIH cost management plan and rigorously reviews each and every application for potential cost savings.

SUCCESS RATES

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Lockshin: To comply with federal mandates, all questions related to race and gender are identified as optional on all research grant applications. As a result, the NIAMS is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. A category denoted as "unknown" represents applicants who chose not to complete the portion of the grant application referring to race and gender. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIAMS' support of minority and women researchers.

COMPETING GRANT SUCCESS RATES FOR MINORITY RESEARCHERS
Fiscal Year 1994

African Americans	14.3
Asian	3.1
Hispanic	17.6
Native American	0.0
Minority	6.6
White	20.1
HBCUs	0.0
Unknown	23.3

COMPETING GRANT SUCCESS RATES BY GENDER

Women	18.3
Male	18.6
Missing*	42.1

*Did not identify gender

AVERAGE COSTS

Mr. Stokes: In real and in constant dollars, what has been the average costs of research project grants awarded to women? To minority researchers? To African American researchers? To HBCUs?

Dr. Lockshin: As stated previously, questions related to race and gender are optional on grant applications. As a result, the following table identifies a category denoted as "unknown" which represents the average cost of competing grants for applications in which gender and race could not be determined. Since there is no way to predict the composition of the applications in the "unknown" category, the following data may not provide a true representation of NIAMS support. The real and constant dollars for women, minority researchers, African Americans, and HBCUs is as follow:

AVERAGE COSTS--CURRENT AND CONSTANT DOLLARS

	1987		1994	
CATEGORY	CURRENT	CONSTANT	CURRENT	CONSTANT
Women	126.0	126.0	200.8	146.5
Minority	149.4	149.4	205.3	149.7
African-American	0.0	0.0	147.5	107.6
HBCUs	0.0	0.0	0.0	0.0
Unknown	305.9	305.9	208.3	151.9

CALCIUM

Ms. Lowey: As you state in your testimony, osteoporosis should be preventable. I am interested in the panel of experts' conclusion that Americans of all ages do not have enough calcium in their diets. Doesn't this merit a public outreach campaign--a campaign to educate Americans about the importance of calcium in the diet? What sort of public education mechanisms exist in this area, and how might NIAMS be more involved in this sort of public education?

Dr. Lockshin: The results of the consensus development conference on Optimal Calcium Intake, released in June 1994, already have spurred several activities. In the private sector, there has been significant newspaper and magazine coverage of the results of the conference. There is already a great deal of public information related to calcium developed by the dairy industry, by food manufacturers that fortify foods, and by companies that produce calcium supplements. Information from the conference is being used and promoted by private voluntary organizations like the National Osteoporosis Foundation and the Older Women's League.

The NIAMS has two information efforts as follow up to the calcium conference. One is through our newly funded Osteoporosis and Related Bone Diseases-National Resource Center. The Resource Center has developed materials that include information from the calcium conference for distribution to the public, patients, and health professionals. For the other information effort, NIAMS is working with the NIH Office of Medical Applications of Research, which co-sponsored the original conference, to develop physician education materials out of the conference results, including a test and a slide presentation, which would result in continuing education credits for participants.

The calcium conference has had other significant impact as well. In terms of public policy, the Food and Nutrition Board of the Institute of Medicine, which previously has directed the process of developing nutrition guidelines, has announced its intent to review the calcium intake guidelines and consider the impact of this nutrient on chronic diseases such as osteoporosis.

The calcium conference results are fostering and influencing research. For example, the NIH Women's Health Initiative will be testing the efficacy of calcium supplements in preventing osteoporotic fractures. The women in the trial will be encouraged to eat a calcium-rich diet and be made aware of both the existing Recommended Dietary Allowances (RDAs) for calcium and the conference results.

The NIAMS is particularly focussed on following up the research gaps that must be addressed before a new government policy on optimal calcium intakes can be derived. In particular, the calcium intake of adolescent females is far below the current RDAs. We have several projects underway to address the calcium requirements of adolescents and young adults. After the conference, NIAMS initiated a project to determine the effect of calcium supplementation on bone mass in young women between the ages of 20 and 30. The data presented at the conference were not direct, but indicated that bone growth is still occurring during this period. An intervention trial conducted in

Nebraska will attempt to confirm this finding. Filling the research gaps through these and other studies will help to strengthen the message to young people to take advantage of the early years to put bone in the "bone bank" to protect against later natural withdrawals.

LUPUS AND WOMEN'S HEALTH

Ms. Lowey: I am pleased to see that NIAMS, the Genome Project, and Office of Research on Women's Health are collaborating on treatment and research on lupus. You say you will be convening a panel of national experts on this issue. Can you tell us more about what you hope to achieve with this group, this work?

Dr. Lockshin: Susceptibility to lupus has been unequivocally established to be an inherited trait, but the exact genes and how they confer susceptibility remain largely unknown. Researchers are making progress, however. They are learning a lot about susceptibility factors from certain strains of specially bred mice that spontaneously develop a lupus-like condition as they mature. Recently, NIAMS-supported researchers in California analyzed 90 percent of the genome of a strain of such mice. They found places on eight different chromosomes to be associated with manifestations of lupus such as abnormal antibodies in the blood, kidney disease, and enlarged spleen. These investigators concluded that the disease features of lupus in mice are affected by distinct, but additive genetic contributions and that the time is ripe to investigate the relevance of this finding to human disease.

NIAMS, together with the National Center on Human Genome Research and the Office of Research on Women's Health, is convening a panel of experts in April 1995. The panel will recommend a research agenda to explore the implications of the recent findings in mice as they relate to lupus in humans. A fuller understanding of genetic susceptibility to lupus could lead to new treatment modalities for those who already have the disease. For those who do not yet have disease manifestations, preventive strategies could be developed.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1996 Budget — Page No.

Organization chart.. 158

Appropriation language.. 159

Amounts available for obligation.. 161

Budget mechanism table.. 162

Summary of changes.. 164

Budget authority by object.. 166

Administrative costs.. 168

Significant items in House and Senate Appropriations Committee Reports................................. 169

Authorizing legislation... 178

Appropriation history... 179

Budget authority by activity.. 180

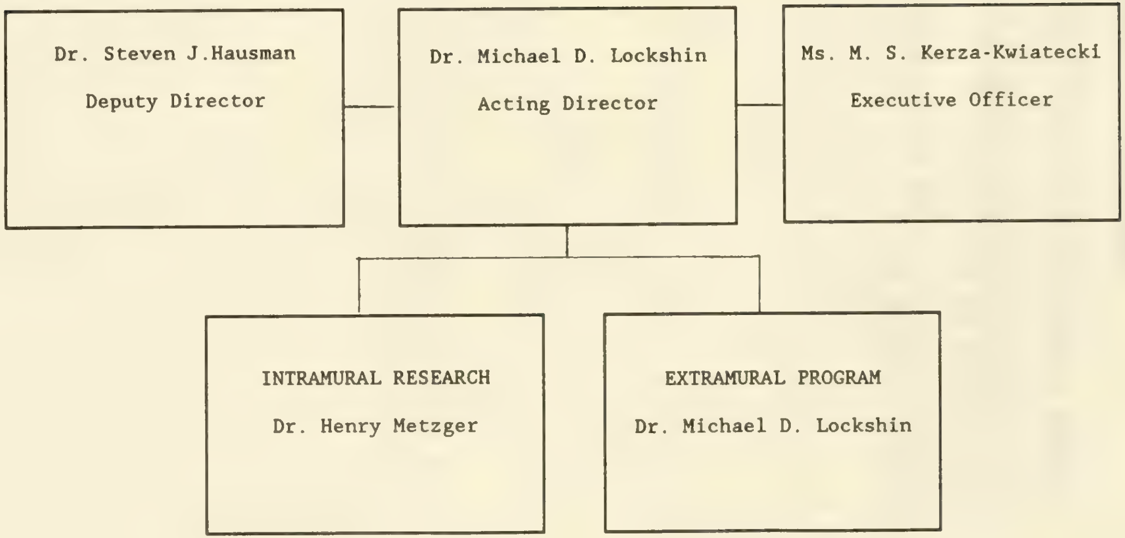
Justification:

A. General statement... 181
B. Extramural research.. 185
C. Intramural research.. 190
D. Research management and support....................................... 192
E. Detail of full-time equivalent employment (FTE)........................ 193
F. Detail of end-of-year employment....................................... 194

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Disease

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to arthritis and musculoskeletal and skin diseases, [$228,521,000] $235,428,000.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation	$223,280,000	$228,521,000	$235,428,000
Recission in accordance with PL 103-211	-76,000	---	---
Section 205 Procurement reduction		-95,000	---
Section 207 Rent reduction		-2,000	
Section 216 S & E reduction		-45,000	---
Subtotal, adjusted appropriation	223,204,000	228,379,000	$235,428,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	-1,501,000		
Comparative transfer from: Other NIH Institutes for Management Fund adjustment	+122,000	+141,000	
Subtotal, adjusted budget authority	221,825,000	228,520,000	235,428,000
Unobligated balance lapsing	-44,000	---	---
Total obligations	221,781,000	228,520,000	235,428,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994--$3,423,000; FY 1995--$4,135,000; FY 1996--$4,135,000.

Also excludes funding for HIV activities: FY 1995--$2,879,000; FY 1996--$3,039,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	500	$107,950,000	493	$112,034,000	467	$109,260,000
Admin. supplements	(13)	329,000	(22)	828,000	(22)	863,000
Competing:						
Renewal	62	14,779,000	59	12,885,000	67	14,941,000
New	113	21,947,000	103	22,427,000	115	26,506,000
Supplements	1	82,000	1	85,000	1	88,000
Subtotal, competing	176	36,808,000	163	35,397,000	183	41,535,000
Subtotal, res. proj	676	145,087,000	656	148,259,000	650	151,658,000
SBIR/STTR	24	2,927,000	22	4,107,000	22	5,260,000
Total, RPGs	700	148,014,000	678	152,366,000	672	156,918,000
Research centers:						
Specialized/comp. centers	30	25,755,000	30	27,008,000	30	28,142,000
Subtotal, centers	30	25,755,000	30	27,008,000	30	28,142,000
Other research:						
Research career programs	68	5,487,000	68	5,487,000	68	5,646,000
Cooperative Clinical Research		0		200,000		206,000
Minority biomedical research support		430,000		452,000		465,000
Other research related	28	2,505,000	27	1,715,000	27	1,765,000
Subtotal, other research	96	8,422,000	95	7,854,000	95	8,082,000
Total, research grants	826	182,191,000	803	187,228,000	797	193,142,000

Training:						
Individual awards:						
Noncompeting	18	493,000	20	547,000	4	77,000
Competing	27	760,000	16	584,000	32	1,087,000
Subtotal, individual	45	1,253,000	36	1,131,000	36	1,164,000
Institutional awards:						
Noncompeting	152	4,601,000	155	4,750,000	107	3,297,000
Competing	41	1,466,000	48	1,704,000	96	3,344,000
Subtotal, institutional	193	6,067,000	203	6,454,000	203	6,641,000
Total, training	238	7,320,000	239	7,585,000	239	7,805,000
Research and development contracts	24	4,502,000	18	5,229,000	18	5,381,000
	FTEs		FTEs		FTEs	
Intramural	69	17,803,000	75	18,210,000	73	18,560,000
Research management and support	81	10,009,000	72	10,268,000	72	10,540,000
Total	150	221,825,000	147	228,520,000	145	235,428,000
Clinical Trials		(5,757,000)		(6,070,000)		(6,270,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

1995 Estimated budget authority	$228,520,000
1996 Estimated budget authority	235,428,000
Net Change	+6,908,000

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase		$5,866,000		+69,000
b. Annualization of January 1995 locality pay		5,866,000		+23,000
c. One more day of pay		5,866,000		+22,000
d. January 1996 pay increase		5,866,000		+96,000
e. Increased cost of centrally furnished services		6,201,000		+375,000
f. Increase cost of service and supply fund		6,143,000		+112,000
g. Increase cost of supplies and materials		6,143,000		+71,000
h. Increase in FECF unemployment compensation		6,143,000		+1,000
i. Decrease in FTS Charges		47,000		-10,000
Subtotal				+759,000
2. Research Management and Support				
a. Within grade increase		5,115,000		+76,000
b. Annualization of January 1995 locality pay		5,115,000		+19,000
c. One more day of pay		5,115,000		+19,000
d. January 1996 pay increase		5,115,000		+82,000
e. Increased cost of centrally furnished services		2,358,000		+197,000
f. Increase cost of service and supply fund		2,795,000		+53,000
g. Increase cost of supplies and materials		2,795,000		+32,000
h. Decrease in Working Capital Fund		199,000		-5,000
i. Decrease in FTS Charges		47,000		-5,000
Subtotal				+468,000

Summary of Changes (con't)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	493	112,034,000	-26	-2,774,000
b. Admin supplements	(22)	828,000	0	+35,000
c. Competing	163	35,397,000	+20	+6,138,000
SBIR/STTR	22	4,107,000	0	+1,153,000
Total	678	152,366,000	-6	+4,552,000
2. Research centers	30	27,008,000	--	+1,134,000
3. Other research	95	7,854,000	--	+228,000
4. Research training	239	7,585,000	--	+220,000
5. Research & dev contracts	18	5,229,000	--	+152,000
	FTEs	Amount	FTEs	Amount
6. Intramural Research Program decrease	75	18,210,000	-2	-409,000
7. Research management and support decrease	72	10,268,000	--	-196,000
Subtotal			-2	+5,681,000
Total changes				+6,908,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	147	145	-2
Full-time equivalent of overtime and holiday hours.................	1	1	0
Average ES salary.....................	$104,397	$108,414	$+4,017
Average GM\GS grade...................	10.1	10.1	0
Average GM\GS salary..................	$44,164	$45,935	$+1,771
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)..	57,756	59,028	+1,272
Average Salary of Ungraded Positions...	52,384	53,536	+1,152
Personnel compensation:			
Full-time permanent..................	$5,464,000	$5,694,000	$+230,000
Other than full-time permanent.......	1,679,000	1,735,000	+56,000
Other personnel compensation.........	351,000	363,000	+12,000
Special personnel service payments...	1,540,000	1,591,000	+51,000
Subtotal, personnel compensation.....	9,034,000	9,383,000	+349,000
Personnel benefits....................	1,872,000	1,936,000	+64,000
Benefits for former personnel..........	75,000	77,000	+2,000
Travel and transportation of persons...	297,000	300,000	+3,000
Transportation of things...............	31,000	32,000	+1,000
Rent, communications, and utilities....	393,000	398,000	+5,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

	1995 Appropriation	1996 Estimate	Increase or Decrease
Printing and reproduction	124,000	131,000	+7,000
Other services:			
Consulting services	258,000	264,000	+6,000
Other	1,868,000	1,924,000	+56,000
Purchases from Govt. Accts	11,548,000	11,646,000	+98,000
Operation of GOCOs	0	0	0
R & D Contracts	4,271,000	4,399,000	+128,000
Supplies and materials	2,111,000	2,138,000	+27,000
Equipment	1,825,000	1,853,000	+28,000
Grants, subsidies & contributions	194,813,000	200,947,000	+6,134,000
Total Budget Authority by Object	228,520,000	235,428,000	+6,908,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)...........	$5,464,000	$5,694,000	$+230,000
Other than Full-time permanent (11.3).	1,679,000	1,735,000	+56,000
Other Personnel Compensation (11.5)...	351,000	363,000	+12,000
Special Personnel Service (11.8)......	1,540,000	1,591,000	+51,000
Total Personnel Compensation (11.9).	9,034,000	9,383,000	+349,000
Personnel Benefits (12.0)..............	1,872,000	1,936,000	+64,000
Benefits for Former Personnel (13.0)....	75,000	77,000	+2,000
Travel (21.0)..........................	297,000	300,000	+3,000
Transportation of Things (22.0).........	31,000	32,000	+1,000
Communications, Utilities, and Miscellaneous Charges (23.3)..........	393,000	398,000	+5,000
Printing and Reproduction (24.0)........	124,000	131,000	+7,000
Consulting Services (25.1).............	258,000	264,000	+6,000
Other Services (25.2)..................	1,868,000	1,924,000	+56,000
Purchases of Goods & Services from Government Accounts (25.3)............	11,548,000	11,646,000	+98,000
Supplies and materials (26.0)...........	2,111,000	2,138,000	+27,000
Total..............................	27,611,000	28,229,000	+618,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
FY 1995 House Report	
Lupus	
1. The House in its report 103-553, page 58, stated: "The Committee strongly encourages NIAMS to continue to support research aimed at identifying the genes and mechanisms which lead to the onset of lupus and organ injury associated with the disease. The Committee also urges NIAMS to continue its focus on research aimed at understanding the gender and ethnic-related factors associated with the high prevalence of this disease in women and minorities. The development of new and innovative treatments is also of great interest to the Committee."	1. NIAMS places a high priority on lupus research, particularly as it relates to understanding the possible genetic and environmental components related to the onset of disease. Several sets of genes associated with abnormal immune responses have been proposed as susceptibility factors in lupus. In April 1995, the NIAMS will convene a panel of national experts in lupus to provide a forum to present the current status of genetic studies of lupus. This workshop will be co-sponsored by the National Center for Human Genome Research (NCHGR) and the NIH Office of Research on Women's Health. In addition, the NIAMS will continue to support a portfolio of research on understanding why this disease is more prevalent in women and black women in particular, as well as to pursue new and innovative treatments for this disease.
Osteoporosis	
2. The House in its report 103-553, page 59, stated: "The Committee recognizes the continuing importance of expanding and intensifying NIAMS research programs investigating osteoporosis,	2. Osteoporosis and related bone diseases continue to be a top research priority for this institute. In June of 1994, the NIAMS sponsored a consensus development conference on optimal calcium intake. The

Item	Action Taken or To Be Taken
which is also part of the Women's Health Initiative."	panel reviewed the latest information and provided recommendations on the optimal calcium intake for children, young adults, postmenopausal women, and the elderly. As a next step in understanding the importance of calcium in building bone, NIAMS will support a clinical trial of calcium supplements in young women. In addition, the NIAMS will fund new research on promising basic cellular, molecular, physiological, and genetic approaches to osteoporosis as a result of the Institute's BONES (Basic Research on Osteoporosis New Experimental Strategies) initiative. The Institute is also collaborating with the Veterans Administration on a study of osteoporosis in men.
Osteoarthritis	
3. The House in its report 103-553, page 59, stated: "The Committee encourages NIAMS to expand its research on osteoarthritis to better understand what triggers this degenerative joint disease so that it can be prevented or detected before significant joint degeneration occurs. Total joint replacement of the hip and knees has been successful in restoring joint function and alleviating the pain associated with osteoarthritis. The Committee encourages expanded research on improved joint implant materials to achieve longer joint replacement life."	3. NIAMS is expanding its research efforts on osteoarthritis. A recent workshop organized by the NIAMS brought together an interdisciplinary group of leading clinicians and scientists to discuss current knowledge and future research directions. The NIAMS and the National Institute on Aging have recently released a request for applications to encourage more research on osteoarthritis, with particular emphasis on understanding the disease processes. With regard to total hip replacement (THR), a panel of experts convened in September 1994 by the NIAMS concluded that THR is a highly successful

Item	Action Taken or To Be Taken
	procedure that has provided relief of pain, increased mobility, and tolerance for activity for thousands of people. Today's implants are quite durable and there is reason to expect that someday artificial hips will last as long as 30 years. There are an estimated 120,000 total hip replacement procedures done annually. This has proven to be a highly cost effective treatment for patients with osteoarthritis of the hip. As a result of a recent biomaterials initiative, NIAMS is supporting four new research projects on the development of improved and longer lasting orthopaedic devices, including total knee and total hip replacements.
Fibromyalgia	
4. The House in its report 103-553, page 59, stated: "...The Committee urges NIAMS to support additional research so that applications not funded under the current RFA may be considered for funding in 1995. The Committee encourages NIH to consider establishing grants to train new investigators in fibromyalgia."	4. Fibromyalgia is the focus of new grants awarded to investigators at five major medical centers across the country. These basic research studies will address questions such as whether people with fibromyalgia have a defect in adrenal hormone production; increase our understanding of specific biologic abnormalities that accompany fibromyalgia; and increase our knowledge of the role the brain plays in the painful symptoms of fibromyalgia. The NIAMS recognizes fibromyalgia is a problem of increasing national importance and concern and welcomes additional research applications on this disorder.

Item	Action Taken or To Be Taken
Low Back Pain	
5. The House in its report 103-553, page 59, stated: "...The Committee encourages NIAMS to continue to develop more accurate diagnostic procedures and non-operative treatments for this problem.	5. About half the adult U.S. population report back pain at some time in their lives. This is a major public health problem and an area of increased research interest. The NIAMS in collaboration with the American Academy of Orthopaedic Surgeons is organizing a workshop entitled "New Horizons in Low Back Pain" to be held November 1-4, 1995. The workshop will focus on three clinical issues: isolated low back pain; low back pain with pinched nerve; and spinal stenosis. Recommendations from the workshop will help NIAMS determine areas to be targeted for additional research.
Connective tissue disorders	
6. The House in its report 103-553, page 59, stated: "...The Committee encourages NIAMS to support additional research on heritable disorders of connective tissue."	6. A planned June 1995 workshop on inherited disorders of connective tissue, sponsored by NIAMS and the Coalition for Heritable Disorders of Connective Tissue, will focus on diseases such as osteogenesis imperfecta, Marfan syndrome, chondrodysplasias, and inherited skin disorders. Following the workshop, NIAMS will develop an initiative to accelerate research on these important diseases of connective tissue.
Alopecia Areata	
7. The House in its report 103-553, page 59, stated: "The Committee is pleased that NIAMS will be cosponsoring an international research workshop	7. At a November 1994 workshop convened by NIAMS, experts exchanged recent research advances on alopecia areata, an immune-mediated disease causing

Item	Action Taken or To Be Taken
on alopecia areata this fall and looks forward to the next advances in finding the cause and cure for this disease."	hair loss. NIAMS will continue its efforts to promote basic research to increase our understanding of alopecia areata.
Foot and ankle complications	
8. The House in its report 103-553, page 59, stated: "The Committee encourages the Institute to consider supporting research needed to improve the diagnosis treatment and management of foot and ankle complications of diabetes and arthritis, as well as other musculoskeletal problems affecting the foot and ankle."	8. The Institute's musculoskeletal diseases branch supports a broad range of research projects on musculoskeletal disorders and conditions, including projects related to foot and ankle complications resulting from injury and disease. In addition, over the past three to four years, NIAMS staff have worked closely with the American Association of Colleges of Podiatric Medicine (AACPM) in organizing a review process for the evaluation of research projects on foot and ankle complications. It is hoped that this effort will provide podiatrists the needed research base to compete for Federal research dollars.
FY 1995 Senate Report	
Osteoporosis	
1. The Senate in its report 103-318, page 94, stated: "The Committee intends that a significant portion of the increased funding for this Institute be used to expand and intensify the research programs for osteoporosis, Paget's disease, osteogenesis imperfecta, and related bone disease."	1. Same response as number 2 in the "1995 House Report."

Item	Action Taken or To Be Taken
Rheumatoid Arthritis	
2. The Senate in its report 103-318, page 94, stated: "...The Committee is pleased to learn that NIAMS will initiate a pilot clinical trial to study the efficacy of intravenous antibiotic therapy in treating rheumatoid arthritis."	2. As requested by the Committee, NIAMS awarded a grant for the conduct of a pilot clinical study designed to test the hypothesis that intravenous antibiotic therapy is an effective and safe treatment for rheumatoid arthritis. In other research areas, NIAMS plans to accelerate research efforts in understanding the role of angiogenesis factor in controlling rheumatoid arthritis and in testing new and innovative immunotherapies for rheumatic diseases. To facilitate research on children with arthritis, NIAMS issued a request for applications for basic research on the pathogenesis of pediatric rheumatic disease.
Osteoarthritis	
3. The Senate in its report 103-318, page 94, stated: "...The Committee urges NIAMS to expand its research in this area in order to better understand what triggers this degenerative joint disease so that it can be prevented or detected before significant degeneration occurs in the affected joints. ... The Committee supports expanded research on better designed implants made of improved materials to achieve longer lasting fixation."	3. Same response as number 3 in the "1995 House Report."
Fibromyalgia	
4. The Senate in its report 103-318, page 95, stated: "The Committee commends the NIAMS for its leadership in	4. Same response as number 4 in the 1995 House Report."

Item	Action Taken or To Be Taken
stimulating research on fibromyalgia through a recent workshop and a request for applications which resulted in 18 research proposals. The Committee urges NIAMS to support additional research so that applications not funded under the current RFA may be considered for funding in fiscal year 1995. The Committee encourages the NIH to consider establishing grants to train new investigators in fibromyalgia."	
Epidermolysis Bullosa	
5. The Senate in its report 103-318, page 95, stated: "The Committee understands that experts recently convened at the International Symposium on Epidermolysis Bullosa (EB) to discuss epidemiology, basic, and clinical science findings. Highlights of the symposium included gene identification in the inherited forms of this disease and analysis of the data from the EB registry. The Committee is pleased to learn of this progress and urges the NIAMS to continue a vigorous research program on this tragic blistering disease."	5. Accelerating research on epidermolysis bullosa (EB) is a research priority for NIAMS. Several years ago it was discovered that in one of the severe forms of EB, a normal structure called an anchoring fibril was missing. In the last few years it has become clear that anchoring fibrils are composed of a type of protein that is abnormal in essentially all forms of dystrophic EB, both recessive and dominant. In addition, the defective genes and abnormal proteins in the most frequently fatal form of EB, called junctional EB, have been found. This work now provides the basis for early (including prenatal) diagnosis and, once technology is far enough advanced, the potential for gene therapy for this devastating disease.
Psoriasis	
6. The Senate in its report 103-318, page 95, stated: "Psoriasis is a chronic skin	6. NIAMS-supported investigators are engaged in research to study the pathogenesis of

Item	Action Taken or To Be Taken
disease characterized by thickened, red areas of skin with silvery scales which afflicts an estimated 4 million Americans. The Committee is excited to learn of research underway to locate the gene for psoriasis, utilizing tissue samples from the National Psoriasis Foundation Tissue Bank. The Committee urges NIAMS to continue this genetic research as well as pursue both basic and clinical studies on the immune response and improved treatments."	psoriasis. With the development of the tools of molecular genetics, it has recently been demonstrated that the gene for psoriasis is located on a portion of chromosome 17 of the human genome. It is of interest that, of the known genes in this area, several have to do with activation of immune cells, leading to new theories of how psoriasis develops. NIAMS will continue to promote this important area of research.
Scleroderma	
7. The Senate in its report 103-318, page 95, stated: "...The Committee encourages the Institute to increase its research into scleroderma and consider convening a workshop to develop a long-range research plan for this disease. The Committee further encourages NIAMS to consider developing a national scleroderma patient registry."	7. The NIAMS recently awarded a contract to Wayne State University to establish a population-based registry for scleroderma in southeastern Michigan. The NIAMS recognizes the need for increased research on this serious rheumatic disease that affects women between the ages of 20 and 50 and will encourage more research in this area.
Lupus	
8. The Senate in its report 103-318, page 95, stated: "The Committee encourages NIAMS to continue to support research aimed at identifying the genes and mechanisms which lead to the onset of lupus and organ injury associated with this disease. The Committee also urges NIAMS to continue its focus on research aimed at understanding the gender and ethnic-related factors associated with the high prevalence of this disease in women and minorities. The development of new and	8. Same response as number 1 in the "1995 House Report."

Item	Action Taken or To Be Taken
innovative treatments is also of great interest to the Committee."	
Skin diseases	
9. The Senate in its report 103-318, page 117, stated: "...The Committee requests the Director to develop a report in time for next year's hearings, regarding skin disease research activities supported by the NIH...."	9. The NIAMS is the lead institute at the NIH for research on skin diseases and was asked by the Director to coordinate the development of this report. The report will be submitted to the committee prior to the hearings.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation......	Section 301	42§241	Indefinite	>$220,935,000	Indefinite	>$227,623,000
National Institute of Arthritis and Musculoskeletal and Skin Diseases................	Title IV Part C	42§285d	Such sums as necessary		Such sums as necessary	
National Research Service Awards	Section 487(D)	42§288	Such sums as necessary	7,585,000	Such sums as necessary	7,805,000
Total Budget Authority....				228,520,000		235,428,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$106,733,000	$140,225,000	$129,475,000	$138,713,000
1988	132,089,000	154,632,000	153,867,000	147,679,000
1989	158,244,000 2/	155,487,000 2/	161,244,000 2/	159,897,000 3/
1990	167,334,000 4/	171,673,000	171,688,000	171,250,000 5/
1990 Sequester				-2,320,000
1991	176,080,000	191,397,000 6/	198,746,000	193,247,000 7/
1991 Sequester				-3,000
1992	204,797,000	204,977,000	203,076,000	203,047,000 8/
1993	214,929,000	214,619,000	214,619,000	212,456,000 9/
1994	210,382,000	223,280,000	223,280,000	223,204,000 10/
1995 11/	228,413,000	227,021,000	229,021,000	228,379,000
1996 11/	235,428,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for AIDS research and education ($687,000).
3/ Excludes funds for AIDS research and education ($673,000), for Gramm-Rudman-Hollings spending targets ($1,943,000), and for the FY 1989 Procurement Reform Reduction ($91,000).
4/ The 1990 request excludes funds for the National HIV program ($1,254,000) proposed consolidation in the Office of the Assistant Secretary for Health.
5/ Excludes enacted administrative reductions of $431,000.
6/ Excludes funds for NRSA training, which is unauthorized.
7/ Excludes enacted administrative reductions of $5,195,000.
8/ Excludes encacted administrative reductions of $1,089,000.
9/ Excludes enacted administrative reductions ($1,717,000), Salaries and Expenses reductions ($441,000), Consultant Services reductions ($5,000), and TB transfer ($209,000).
10/ Excludes enacted administrative reductions of $142,000.
11/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Changes	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Arthritis and musculoskeletal and skin diseases........		$177,138		$183,357		$193,969		$200,042		$206,328		+$6,286
Intramural research....	85	15,171	82	17,259	69	17,803	75	18,210	73	18,560	-2	+350
Research management and support..........	82	9,513	84	9,832	81	10,009	72	10,268	72	10,540	--	+272
Subtotal, obligations	167	201,822	166	210,448	150	221,781	147	228,520	145	235,428	-2	+6,908
Unobligated balance lapsing..............		31		39		44		---		---		
Total, Budget Authority	167	201,853	166	210,487	150	221,825	147	228,520	145	235,428	-2	+6,908

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
150	$221,825,000	147	$228,520,000	145	$235,428,000	-2	+$6,908,000

General Statement

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) continues to make progress in the fight against rheumatic, musculoskeletal, and skin diseases. The Institute leads the Federal biomedical research effort in these fields by conducting research, research training, and clinical trials and by disseminating information on research results. The diverse diseases under the mandate of the NIAMS include many of the most long-lasting, disabling, and costly conditions affecting our Nation. Nearly every household is affected: every age, every race, and both genders. Some NIAMS diseases disproportionately affect women, minorities, children, the elderly, and athletes. Moreover, as more Americans live longer, the prevalence of these diseases will rise and place an even greater burden on the health care system.

The areas under the broad mandate of the NIAMS are rich in opportunity and ripe for investment. Basic research explains several of the fundamental areas that link NIAMS diseases--such as defects in genes for and the structural proteins of bone, cartilage, and skin; common mechanisms of autoimmunity; and factors that promote inflammation of joints and other tissues. Epidemiology identifies trends of disease, defines populations at risk, and suggests what factors play a role. Clinical research sorts out the true effectiveness of treatments--drugs, surgery, and other means--against the many chronic diseases that NIAMS studies.

The term "arthritis," which literally means joint inflammation, refers to over 100 rheumatic diseases that attack the joints and connective tissues. More than 37 million Americans--one in seven--have some form of arthritis or other rheumatic disease. As the Nation's population ages, the percentage of Americans who suffer from arthritis increases, and it will rise even more over the next 25 years. The NIAMS National Arthritis Data Workgroup estimates that by the year 2020, one in five of our Nation's citizens will be affected by these debilitating diseases.

The economic costs of joint and related rheumatic diseases are staggering. Direct costs of medical care combined with indirect costs, such as those due to lost wages, amount to $55 billion per year. Investments in research to diminish disease and disability will not only alleviate the economic burden of these disorders on the Nation but will improve the quality of life of those afflicted.

An exciting discovery about rheumatoid arthritis (RA) occurred recently. The development of markedly swollen joint tissue that is characteristic of RA depends on angiogenesis, the formation of new blood vessels. NIAMS-supported researchers have produced a novel angiogenesis inhibitor that can slow and even prevent the chronic inflammation of arthritis in several experimental disease models. The inhibitor is currently undergoing preliminary clinical trials, and the Institute plans to expand its efforts in this field. Better understanding of angiogenesis, its role in destructive diseases such as RA, and the effects of angiogenesis inhibition could provide effective means to manage a wide range of joint problems.

RA and several other rheumatic disorders are autoimmune diseases. These occur when the body's immune system goes awry and attacks its own tissues. Research demonstrates the likelihood that a specific set of genes will predict the predisposition to develop autoimmune diseases. The NIAMS will collaborate with the National Center for Human Genome Research (NCHGR) to target autoimmunity genes. Success in this effort will be a breakthrough in understanding RA, systemic lupus erythematosus, scleroderma, and other chronic autoimmune diseases. In addition, the NIAMS, NCHGR, and the Office of Research on Women's Health will convene a panel of national lupus experts in April 1995 to provide a forum to present the current status of genetic studies of lupus both in mice and humans.

Much of musculoskeletal disability results from the bone-thinning disease of osteoporosis and from impairments of the back and spine. These illnesses take an escalating toll on America as its age profile changes. An estimate of the economic costs of musculoskeletal disability is $71 billion annually. A major goal of NIAMS-supported research is to reduce the financial burden, the physical infirmity, and the impaired quality of life caused by crippling disorders.

In groundbreaking research reported last year, NIAMS investigators found a gene that may identify individuals at high risk for osteoporosis. The Institute now coordinates international efforts to have other laboratories confirm this finding. Early results are contradictory, suggesting that differences may be attributable to ethnic differences among the populations studied. The opportunity is to define in what populations the gene is operative so that preventive interventions can be instituted early in life.

Another chronic disorder of great concern to the Institute is low back pain. This frequently reported musculoskeletal problem occurs in persons without apparent cause or in persons with structural abnormalities, injuries, or disease of the back. It is an expensive condition, costing $16 billion in medical treatments and disability payments annually. The cost to the economy in terms of lost workdays is billions of additional dollars. The NIAMS is committed to stimulating basic research in this field.

Skin diseases cause both physical and psychological suffering. These include blistering diseases such as epidermolysis bullosa, scaly disorders such as ichthyosis, inflammatory skin diseases such as psoriasis, pigmentation disorders such as vitiligo, and disorders of hair such as alopecia areata. Most of these conditions are chronic, and their impact is surprisingly significant--each year one in three Americans has a skin disorder that warrants a doctor visit.

The NIAMS devotes a major effort to wound healing. Abnormalities in this process are the basis for many conditions including bedsores, a major concern of the elderly; diabetic and vascular ulcers; burns; surgical trauma; and scarring. Since the cost of healing one bedsore for one patient may be as much as $40,000, better control of wound healing has great potential for savings.

The Institute also focuses on contact dermatitis, a common disease that can be a hazard for all individuals. Contact dermatitis can be allergic in nature such as that caused by poison ivy, or irritant, which is an inflammatory but nonallergic condition such as that caused by industrial chemicals. The latter accounts for a large percentage of occupational disease. Both can have an important effect on quality of life. Recognizing the growing importance of contact dermatitis to the public, the NIAMS, in cooperation with several other interested organizations, will attempt to stimulate research by convening a panel of experts to discuss research opportunities on the causes and progression of the disease. Better understanding in these areas could lead to improved treatments and preventive strategies for contact dermatitis.

A recent finding by NIAMS intramural scientists on how the pathway of a major virus (herpes simplex virus I) is assembled has enabled them to take the virus apart and reconstruct it. NIAMS investigators are now working on understanding exactly how this virus attaches to cells so that they can develop procedures to intervene and prevent its infectivity. In other intramural research, investigators discovered a defect in the body's stress control mechanism in patients with fibromyalgia, demonstrating concretely a physiologic basis for this puzzling disorder.

As we approach the next century, the NIAMS has tremendous optimism that its research investments will pay off in reduced financial costs to society and better lives for those suffering from rheumatic, bone, musculoskeletal, muscle, and skin diseases. The NIAMS will continue to pursue research opportunities in areas that show great promise for advancements in understanding, treatment, and prevention of the many common and chronic diseases of its mandate.

Purpose and Method of Operation

Extramural research and training are supported through five program areas: arthritis, bone biology and bone diseases, musculoskeletal diseases, muscle biology, and skin diseases. Funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at three research laboratories and one clinical research branch. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

The President's appropriation request of $235,428,000 for this account represents current law requirements. No proposed law amounts are included.

Funding for the National Institute of Arthritis and Musculoskeletal and Skin Diseases during the last five years has been as follows:

	Amount	FTE
FY 1991	$191,833,000	140
FY 1992	201,853,000	167
FY 1993	210,487,000	166
FY 1994	221,825,000	150
FY 1995	228,520,000	147

Overall Budget Policy

The FY 1996 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases is $235,428,000, an increase of $6,908,000 over the comparable FY 1995 level of $228,520,000. The request includes 145 FTEs, a reduction of 2 FTEs from the FY 1995 level. At the FY 1996 request level, the Institute will support 467 noncompeting research project grants at a level of $109,260,000 and 183 competing grants at a level of $41,535,000 compared to 493 and 163, respectively in FY 1995. The FY 1996 request includes $28,142,000 for 30 research centers, $8,082,000 for other research, $7,805,000 for research training, and $5,381,000 for R&D contracts. Intramural research will be conducted at a level of $18,560,000 compared with $18,210,000 in FY 1995. Research management and support activities will be funded at a level of $10,540,000 compared to $10,268,000 in FY 1995.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$194,013,000	$200,042,000	$206,328,000	+$6,286,000

The NIAMS has primary responsibility at the National Institutes of Health for extramural research and research training in arthritis, bone biology and bone diseases, musculoskeletal diseases, muscle biology, and skin diseases.

Funding for the Arthritis and Musculoskeletal and Skin Diseases Program during the last five years has been as follows:

	Amount
FY 1991	$168,655,000
FY 1992	177,169,000
FY 1993	183,357,000
FY 1994	194,013,000
FY 1995	200,042,000

Rationale for the Budget Request

With the FY 1996 extramural request these funds will provide support for the following activity: Arthritis and Musculoskeletal and Skin Diseases Program, $206,328,000, an increase of $6,286,000 or 3.1 percent over the FY 1995 estimate of $200,042,000. Following are selected examples of current research activities and plans for FY 1996 based on the request level:

Systemic Lupus Erythematosus (SLE) - SLE is a serious autoimmune disease that disproportionately affects women, especially African-American women. An exciting new avenue of research indicates that lupus may involve defects in a process by which the body eliminates unnecessary, damaged, or potentially harmful cells. This process is known as programmed cell death, or "apoptosis." In the immune system, apoptosis is responsible for eliminating white blood cells with the potential to react against the body's own tissues. Normally, the immune system detects these "self-reactive" cells, and they are destroyed by apoptosis before they can do any harm. If the process of apoptosis is defective, self-reactive cells will survive and may cause autoimmune diseases such as lupus.

Recent NIAMS-supported studies show that in a mutant mouse strain that develops a lupus-like illness, one of the genes that control programmed cell death is defective. When this defective gene, called Fas, is replaced with a normal Fas gene, the mice no longer develop signs of lupus. Preliminary research suggests that defects in apoptosis may also occur in people with lupus. Better understanding of the role of apoptosis may lead to new treatments targeted to specific defects in lupus. NIAMS will also continue to support research on the molecular causes of lupus, and basic and clinical research on why the disease is more prevalent in certain populations.

Arthritis in Children - The rheumatic diseases of childhood include juvenile rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, and vasculitis. They present unique clinical and research challenges. Combined, the rheumatic diseases are the most common form of chronic diseases of childhood, and they are major causes of disabilities. The pediatric forms of rheumatic disease differ clinically from their counterparts in adults. Current evidence suggests that the underlying mechanisms leading to disease may be different as well.

The status and future direction of pediatric rheumatology was the subject of a workshop sponsored by the NIAMS. Nationally recognized clinicians and scientists in the field of pediatric rheumatic diseases met to identify research opportunities that can be addressed with current methodologies. The group recommended the creation of disease registries and emphasized the need for a basic research base to advance understanding of the diseases.

Following this panel's recommendations, the NIAMS issued a request for applications (RFA) in FY 95 for basic research projects on the pathogenesis of pediatric rheumatic diseases. The goal of the RFA is to promote research on the genetic bases and on the immunologic and biochemical mechanisms leading to pediatric rheumatic diseases. The research will seek to identify critical processes that can be pursued to develop new and effective treatments. The RFA strongly encourages multidisciplinary approaches and collaborations between basic scientists and pediatricians.

Innovative Therapies in Rheumatic Diseases - Development of a new class of agents known as biologics, availability of technology to produce molecules that can control immune and inflammatory responses, and improved understanding of rheumatic diseases have led to a surge of innovative therapies for these disorders. NIAMS-sponsored research has provided the required background. Technology transfer occurs through the sponsorship of the private sector and the Food and Drug Administration (FDA). Through this cooperation, many new agents are now being tested for safety and efficacy in patients with rheumatoid arthritis and systemic lupus erythematosus.

Although the results of some trials have been promising, increased support for basic research that explains the mechanisms by which these therapies work is critical to designing improved treatments. In addition, there remain many opportunities to gain further insights by studying individual responses under controlled experimental treatments.

As an innovative way to link basic and clinical research, the NIAMS will support small basic research projects linked to ongoing clinical trials. The object is to learn about the diseases by studying patients undergoing the innovative immunotherapies. Investigators will conduct pilot research projects that will provide preliminary data to enhance ongoing trials and to suggest new research directions.

Osteoporosis - Prevention of osteoporosis focuses on building the largest possible bone mass and maintaining these levels with minimal bone loss. Adequate calcium and other nutritional intake coupled with an exercise program may provide the most practical approach to prevention. A panel of experts convened by the NIAMS to evaluate data on optimal levels of calcium intake concluded that Americans of all ages are not receiving enough calcium in their diets. The purpose of the NIH Consensus Development Conference on Optimal Calcium Intake, held in June 1994, was to evaluate the available data on calcium as it relates to health, particularly building and maintaining healthy bones. The panel made specific recommendations for the amount of calcium that should be consumed daily by each segment of the population, including children/young adults, men, and women (both pre- and post-menopausal). The NIAMS will focus on innovative approaches to disseminate these findings to help reduce--through prevention--the health and cost burdens endured by those with osteoporosis. The Institute will also continue to pursue research opportunities in the areas of bone structure, formation, remodeling and repair.

Osteoarthritis - Osteoarthritic diseases are the most prevalent disorders of the joints, with x-ray evidence seen in at least 70 percent of the population over age 65. The economic cost of osteoarthritis is estimated to be at least $8 billion excluding indirect costs. In many cases the initiating event and the pathology of disease progression are not easy to determine. Common elements among the diseases are deterioration of cartilage, the bone that underlies it, ligaments, and other adjacent tissues.

Experts in the field convened in a workshop entitled "New Horizons in Osteoarthritis" in April 1994. This meeting brought together an interdisciplinary group of leading clinicians and scientists to discuss current knowledge and to recommend future research directions. The NIAMS organized this effort along with co-support from the National Institute on Aging and the American Academy of Orthopaedic Surgeons. A book that summarizes the state-of-the-art research will be published in February 1995. In October 1994, the NIAMS and the NIA released a request for applications, based on the workshop's recommendations, to encourage more basic research on this topic of high public health impact.

Total Hip Replacement - More than 120,000 artificial hip joints are implanted annually in the United States. As the population ages, hip replacement will play an increasingly prominent role. To promote the satisfactory replacement of deteriorated and severely injured hips, the NIAMS helped organize the NIH Consensus Development Conference on Total Hip Replacement, held in September 1994. The consensus panel concluded that a type of hip replacement known as a hybrid--because it has both a cemented and a noncemented part--ensures the best long-term outcomes. Further research on the inflammatory response caused by debris from hip replacement devices was recommended. NIAMS scientists will continue to investigate optimal designs and materials that will permit mobility and comfortable independent living.

Orthopaedic Biomaterials - Orthopaedic implants are commonly used in the treatment of musculoskeletal diseases and injuries. One major class of orthopaedic devices, used for fixation, includes pins, screws, wires, plates, and rods. The other large class consists of joint replacement devices, the most common of which are for hips and knees. Although these orthopaedic devices have had great general success in reducing the morbidity and disability that result from musculoskeletal disorders, some devices become loose after time, requiring repeat surgery. These repeat surgeries are costly to perform and are not likely to be as successful as the original procedures.

In an effort to combat escalating health care costs and to improve care of patients, the Institute has established a special research initiative in orthopaedic biomaterials that is a multidisciplinary approach combining advances in mechanical science with advances in biology. Public health cost savings and the quality of life of recipients could be significantly increased by more effective, longer lasting orthopaedic devices.

Repetitive Motion Injuries - Repetitive motion injuries are increasing. According to the Center for Workplace Health, almost 2 million Americans suffer symptoms of the repetitive motion injury known as carpal tunnel syndrome. An additional 4 million American workers have tendinitis, most often in the wrists and arms. Recognizing the magnitude of the problem, the NIAMS assembled a team of nationally recognized researchers on repetitive motion disorders in June 1994. The proceedings of the meeting will be published in the spring of 1995 and should serve as a stimulus for further research.

Muscle Fitness and Exercise - Millions of Americans have sedentary occupations and do not participate in regular exercise programs. Muscle weakness occurring in these individuals can lead to loss of normal muscle function and increased risk of injury. Furthermore, muscle weakness increases the risk that men and women with diseases such as arthritis and osteoporosis will fall and suffer injury. The metabolism and protein composition of skeletal muscle change profoundly when muscle use is altered, either by immobilization or increased exercise. With immobilization, muscle wasting is extremely rapid; changes due to increased use occur more slowly. While total changes in muscle have been well observed by researchers, details regarding the process of muscle wasting will be the subject of ongoing and future studies.

Muscle Injury and Repair - Injury to skeletal muscle can occur during normal activities, under conditions of high activity, during work or sports, or as the result of trauma or disease. Muscle tears can cause long term disability, including permanent loss of muscle tissue. Researchers will continue to investigate the biological and mechanical correlates of strain injuries, which have a tremendous impact on vocational and sports medicine. Other studies will focus on the muscle-tendon junctions since these regions are especially prone to injury. In addition, important research will be pursued to assess risk factors, such as fatigue, and the usefulness of activities that may be helpful in preventing muscle injury, including stretching, warmup, and passive muscle manipulations.

Muscle regeneration is influenced by the initial process by which it was damaged. Cells from which new muscle grows are attracted to the site of injury by substances known as inflammatory mediators. The new tissue generated is scarred and weakened compared to the original. The mechanisms that control both degenerative and regenerative processes are not completely characterized. Topics that will be the subjects of future studies include physiological consequences of muscle stretch and injury, relationship between the site and type of muscle injury, distinction between overuse and growth stimulation, and physiological properties of regenerated muscle.

Genetics of the Skin - The field of molecular genetics of the skin has seen major scientific advances over the last 10 years. Molecular genetics has proven to be of tremendous value in understanding a number of skin diseases and is being actively studied in other skin diseases in which the etiology is unclear. A large portion of the NIAMS skin disease research portfolio is devoted to understanding skin structure, function, and disease via molecular genetics.

Epidermolysis bullosa (EB) represents a group of genetic diseases that function as prototypes in modern molecular genetic investigations in skin disease. The various EB diseases cause blistering in different parts of the structure that joins the inner (dermal) and outer (epidermal) layers of skin. Investigators have found several abnormal genes that code for the structural proteins within these zones.

Similarly, several forms of ichthyosis have been targeted for molecular genetic investigations of the keratins--the major proteins of skin--that are important in the upper layers of the epidermis. Genetic defects in two of these keratins, types 1 and 10, underlie a form of ichthyosis called epidermolytic hyperkeratosis. Similar types of investigation have uncovered the molecular and genetic defects in albinism, Marfan syndrome, and Ehlers Danlos syndrome. Once genetic defects that cause disease are identified, scientists can attempt to correct the defect through gene therapy. Gene therapy strategies are in the early stages of development and offer exciting research opportunities.

With the development of tools of molecular genetics, researchers are also gaining new knowledge about psoriasis, a common skin disease affecting approximately two percent of the population. Molecular genetic studies are being applied to tissue samples from affected families collected by the National Psoriasis Foundation-funded tissue bank, an effort stimulated by a joint workshop with the NIAMS a few years ago. NIAMS-supported investigators have recently reported that in the familial groupings examined, psoriasis was associated with a portion of the human genome. Once the area of the human genome that is linked to the disease is more clearly defined, the next challenge is to find the specific gene, the defect, and the way in which the defective gene product, that is a protein, results in disease. Therapeutic approaches can then be designed to correct either the abnormal gene or its effects.

The skin provides an ideally accessible location for approaches such as gene therapy, which can be used for both the treatment of skin disease and also for the treatment of diseases of other organ systems. The latter is accomplished by using the skin to manufacture normal or missing proteins throughout the body. Major advances have occurred in the design of delivery systems that provide for sustained release of drugs through the skin. There are research opportunities to explore further new means of direct delivery through the skin, and delivery via a "gene gun," a technique in which epidermal stem cells act as carriers for human genes used to treat skin and systemic diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
69	$17,803,000	75	$18,210,000	73	$18,560,000	-2	+$350,000

Four major units carry out the research conducted within the NIAMS Intramural Research Program. These include the Arthritis and Rheumatism Branch, the Laboratory of Physical Biology, the Laboratory of Structural Biology Research, and the Laboratory of Skin Biology.

Funding for the Intramural Research Program during the last five years has been as follows:

	Amount	FTE
FY 1991	$14,349,000	70
FY 1992	15,171,000	85
FY 1993	17,298,000	82
FY 1994	17,803,000	69
FY 1995	18,210,000	75

Rationale for the Budget Request

The FY 1996 budget request for the Intramural Research Program is $18,560,000, an increase of $350,000 or 1.9 percent over the FY 1995 estimate of $18,210,000. The following outlines some of the ongoing research activities and future research directions of the NIAMS Intramural Research Program:

Skin Biology/Skin Diseases - The body's largest organ is the skin, which protects the internal organs from the environment. The outermost layer of the skin is the epidermis, consisting of cells that resemble porous stones when viewed under the microscope. The major components of these cells are a class of proteins known as fibrous keratins, which are retained in a tough, insoluble cell envelope.

Intramural scientists have been studying the genetic defects responsible for the ichthyoses, a group of scaling diseases of the epidermis. Two years ago they discovered that genetic defects in a fibrous keratin protein causes one of the diseases in this group, epidermolytic hyperkeratosis. More recently, they identified the genetic defect of another disease, lamellar ichthyosis. These diseases are characterized by thickening, scaling, and blistering of the outer skin. In newborns with these diseases, even light pressure on the skin from a diaper can cause blistering. These babies' fragile, blistered skin makes them susceptible to infection--and sometimes death.

To understand better the genetic defects, the research team is beginning to explore how normal epidermis is assembled and holds together. For example, they have learned how the complex amalgam of keratin proteins that form the cell envelope are assembled and joined together and how this process is integrated with the major set of fibrous proteins of the epidermal cells. Our scientists have developed a hypothetical model for assembly of the cell envelope of the outer skin that will enable them to investigate the development of common disorders such as psoriasis.

Fibromyalgia - Fibromyalgia (FM) has been estimated to affect approximately 3 to 6 million Americans, the majority of whom are women. The 1990 American College of Rheumatology criteria classify a person as having FM if symptoms of widespread pain are present and physical examination demonstrates 18 tender points in specific locations on the body. FM sufferers usually have prominent fatigue, difficulty sleeping, and other symptoms.

Various studies have suggested the FM is associated with stress. The stress response occurs through complex interactions among a number of systems in the body. A pivotal aspect of stress response is the interactions that occur among the hypothalamus located in the brain, the pituitary gland that is attached to it, and the adrenal glands located just above the kidneys. These constitute the hypothalamic-pituitary-adrenal (HPA) axis. In stress situations the hypothalamus produces a first hormone. This hormone in turn stimulates the pituitary gland to produce a second hormone that in turn stimulates the adrenal glands to produce a third hormone, the well-known cortisone.

NIAMS scientists recently published findings indicating that patients with FM have too little cortisone in their urine specimens. However, in these patients the pituitary responds normally to the first hormone, indicating that the defect occurs in the ability of the adrenal glands to respond to the second hormone. These investigations are a step toward better understanding of the physical basis of FM.

Cell Signaling - Immunoglobulin E (IgE) is an important antibody in the immune system. The receptor for IgE is located on the surface of connective tissue cells, which are found throughout the body. When IgE binds to them, these receptors play a key role in the secretion of substances that control inflammation. IgE receptors also play a role in extracellular-intracellular communications, a research area that intramural scientists are currently pursuing.

Through genetic manipulations carried out in the laboratory, NIAMS intramural scientists have been able to develop a cell line with IgE receptors that function like IgE receptors on human cells. They are exploring how the IgE receptor functions as a transmembrane signaling molecule, communicating information about the outside environment to the cell's interior. This research is germane to the whole range of body processes that regulate cell metabolism.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
81	$10,009,000	72	$10,268,000	72	$10,540,000		+$272,000

The Research Management and Support (RMS) activity provides the staff and resources necessary to support the overall administration and coordination of the managerial and scientific programs of the Institute. Staff included in RMS provide direction for scientific programs, evaluate research needs, develop program announcements, manage the review and award of grant and contract applications, and support and monitor funded research projects. RMS also supports staff to manage and direct equal employment opportunity issues. Other principal functions under this activity include planning, policy development, financial management, personnel management, information dissemination, data processing, procurement, and property management.

Funding for the Research Management and Support activity during the last five years has been as follows:

	Amount	FTE
FY 1991	$8,829,000	70
FY 1992	9,513,000	82
FY 1993	9,832,000	84
FY 1994	10,009,000	81
FY 1995	10,268,000	72

Rationale for the Budget Request

The FY 1996 budget request for Research Management and Support is $10,540,000, an increase of $272,000 or 2.6 percent over the FY 1995 estimate of $10,268,000.

These funds will be used to support the Office of the Director and the Extramural Program. The Office of the Director provides the guidance and professional leadership needed to manage the Institute. Within the Office of the Director are the various administrative management offices which provide advice to the Director and his staff, and direct the administrative functions of the Institute. The Extramural Program comprises the professional and support personnel who are responsible for administration of the Institute's grant and contract activities.

Also supported by the RMS activity are the Office of Scientific and Health Communications which serves as the focal point for most of the public information campaigns; the Office of Disease Prevention, Epidemiology, and Clinical Applications; and the Office of Program Planning and Evaluation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Full-time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	44	39	39
Extramural Program	37	33	33
Intramural Research	69	75	73
Total	150	147	145

Average GS/GM Grade

1991	10.1
1992	9.6
1993	10.5
1994	10.1
1995	10.1
1996	10.1

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

194

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Estimate
ES-5	1		
ES-4	1	1	2
ES-2	1	1	1
Subtotal	3	2	3
Total - ES Salary	$316,500	$208,794	$325,241
GS/GM-15	14	14	14
GS/GM-14	16	16	15
GS/GM-13	6	6	6
GS-12	17	17	17
GS-11	8	8	8
GS-10	1	1	1
GS-9	5	5	5
GS-8	5	5	5
GS-7	24	26	24
GS-6	5	5	5
GS-5	3	3	3
GS-4	7	7	7
GS-2	2	2	2
Subtotal	113	115	112
Grades established by Act of July 1,1944 (42U.S.C.207):			
Assistant Surgeon General	5	5	5
Full Grade	2	3	3
Subtotal	7	8	8
Ungraded	25	25	25
Total permanent positions	114	116	115
Total positions, end of year	148	150	148
Total full-time equivalent(FTE) employment, end of year	150	147	145
Average ES level	3.7	3	3.3
Average ES salary	$105,500	$104,397	$108,414
Average GM/GS grade	10.1	10.1	10.1
Average GM/GS salary	$44,065	$44,164	$45,935

TUESDAY, MARCH 21, 1995.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

WITNESSES

DR. JAMES B. SNOW, DIRECTOR
DR. JAY MOSKOWITZ, DEPUTY DIRECTOR
DR. JAMES BATTEY, SCIENTIFIC DIRECTOR
W. DAVID KERR, EXECUTIVE OFFICER
PATIENCE T. SPARKS, BUDGET OFFICER
DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. Next, the National Institute on Deafness and Other Communication Disorders; we're pleased to welcome you, Dr. Snow.

I also might say that we understand that this is Dr. Moskowitz' last appearance before our subcommittee. He's served for 26 years in many capacities, and we've certainly enjoyed working with him. And Dr. Moskowitz, we want to wish you very well. We understand you're taking a deanship at Wake Forest University, and we wish you well in that.

Dr. MOSKOWITZ. Thank you, Mr. Chairman. I must say that it's been an absolute privilege for me to serve the American public at the National Institutes of Health. It's one of the most noble institutions in this world, and I really enjoyed it. I enjoyed working with this committee, and I support everything that you've done as Chairman of this committee, and I support everything that the leadership of NIH has done over the years. It's been an absolute joy for me, and I've seen years of accomplishment. And I hope that these successes continue into the future.

Mr. PORTER. Well, those are very nice comments. I hope that we can continue to provide the kind of support to NIH that it very much needs. I think the money, I've said it very often, is perhaps better spent at NIH than anywhere else in all of government. And we value the service of people like yourself who come here to work at the Institute and provide your expertise to the American people.

Thank you for your service, and again, we wish you well.

Dr. Snow, it looks like you have done a lot of homework there. That's about the thickest briefing book I've ever seen. [Laughter.]

Why don't you introduce the rest of the people at the table and proceed.

INTRODUCTION OF WITNESSES

Dr. SNOW. You know Dr. Ruth Kirchstein, the Deputy Director of the NIH; Mr. Bill Beldon of the Department; Dr. Moskowitz, the

Deputy Director of the NIDCD; and Mr. W. David Kerr, the Executive Officer of the NIDCD.

I'm very pleased to introduce to you Dr. James F. Battey, the new Scientific Director of the NIDCD. Dr. Battey is a distinguished molecular biologist and brings extraordinary expertise in molecular biology to research in human communication.

And you know Ms. Patience T. Sparks, the Budget Officer of the Institute.

OPENING STATEMENT

Mr. Chairman, thank you for the opportunity to appear before the committee. Forty-six million Americans are disadvantaged economically, educationally, professionally and socially by diseases that interfere with their hearing, balance, smell, taste, voice, speech and language. These diseases are often chronic, resulting in lifelong disability.

I am delighted to report to you today of the gene responsible for Usher's syndrome, which causes deafness and blindness. This discovery was made possible by the Usher's Syndrome Consortium, an international group of investigators brought together by the NIDCD. This month, they reported in the journal Nature the identification of the gene. NIDCD supported scientists at Boys Town National Research Hospital as well as British, Dutch and French investigators collaborated on this important discovery.

Molecular biology and molecular genetics are also providing solid advances in such disorders as Crouzon syndrome. Crouzon syndrome is a hereditary disorder in which the bones of the skull fuse prematurely. This prevents the growth and development of the brain; it causes the eyes to bulge, hearing impairment, and mental retardation. A NIDCD-funded team has now mapped the gene to a small area of chromosome 10. With cloning and chemical characterization of this gene, diagnosis can be made earlier and intervention can be carried out before any damage occurs.

Extraordinary progress has occurred in locating the genes responsible for syndromes of hearing impairment and dominant, x-linked and mitochondrial nonsyndromic hearing impairment. The problem is that 80 percent of congenital and early onset hearing impairment is nonsyndromic and recessively inherited. And it's been possible to find the genes for this recessive nonsyndromic hearing impairment only in isolated populations. None have been found in unisolated populations such as the United States.

To expedite research in recessive nonsyndromic hearing impairment, the NIDCD has established the Hereditary Hearing Impairment Resource Registry, and a consortium, like the Usher's Syndrome Consortium, to encourage the sharing of molecular genetic and clinical data. With analysis of these data, finding genes responsible for hearing impairment will be accelerated.

In view of the difficulty of finding genes for recessive nonsyndromic hearing impairment, the intramural program is enhancing its investigative approach under the leadership of Dr. Battey. The approach of using linkage analysis in searching for a gene does not always lead directly to cloning the gene, because the number of individuals in a family is so small.

However, using a mouse mutant model has the advantage of generating hundreds of meioses from a single set of parents. This eliminates the problem of genetic heterozygosity inherent in human linkage studies. Complementing human studies by using animal models offers a systematic way to search for the genes in unisolated population.

It is just this sort of complementary investigation that led to the exciting discovery of the Usher gene. The NIDCD has intensified its efforts to develop vaccines against otitis media. Middle-ear infections are the major cause of visits to emergency rooms and physicians offices for young children. The pneumococcus and the nontypeable Haemophilus influenzae are the two major pathogens that cause otitis media. Stage I and stage II clinical trials for vaccines against the pneumococcus are underway.

Our strategy includes conjugating an oligosaccharide with a protein, as was successfully done with the Haemophilus influenzae type B vaccine against meningitis in young infants.

In research on smell and taste, there have been both basic and clinical advances. Contemporary imaging and molecular biological techniques applied to biopsies of the olfactory sensory tissue have proved useful in the early diagnosis of Alzheimer's disease. The olfactory neurons in Alzheimer's disease are the only affected neural tissue that can be easily obtained for study from living patients. The molecular pathogenesis of Alzheimer's disease is being diligently pursued by NIDCD scientists.

Clinical progress has also been made by NIDCD taste scientists on the reduction of mouth pain in cancer patients who have undergone chemotherapy or radiation therapy. This pain is demoralizing, as it affects speaking, swallowing, and nutritional status. Working to alleviate this side effect of needed therapy, scientists combined capsaicin, the hot ingredient in chili peppers, with taffy. This capsaicin-laced candy reduces oral pain for these individuals for several hours at a time.

The NIDCD has entered its seventh year. We are initiating a new level of planning to make certain that the right mix of scientific expertise is being supported to take maximum advantage of the research opportunities in human communication. The needs of 46 million Americans are constantly before us. We have the leads, the scientific talent and the tools of molecular biology, molecular genetics, informatics and imaging to find the causes and improve the prevention and management of the diseases of the most human of attributes, communication.

The fiscal year 1996 budget request is $172,399,000. I am happy to try to answer any questions that you have.

[The prepared statement and biography of Dr. James Snow follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute on Deafness and Other Communication Disorders

Mr. Chairman, thank you for this opportunity to appear before the committee.

Mr. Chairman and members of the committee, 46 million Americans are disadvantaged economically, educationally, professionally, and socially by diseases that interfere with human communication. The majority of these 46 million persons are our children and our elderly. These individuals have disorders of hearing, balance, smell, taste, voice, speech and language; many of which are chronic and result in lifelong disability.

Scientists supported by the NIDCD are approaching these problems with the most modern technologies available. Molecular biology and molecular genetics are providing solid leads in such disorders as Crouzon syndrome. Crouzon syndrome is a hereditary disorder in which the bones of the skull fuse prematurely. This prevents the growth and development of the brain and causes the eyes to bulge, hearing impairment and mental retardation. Until recently, we only knew that it was recessively transmitted, but an NIDCD-funded team has now mapped the gene to a small area on chromosome 10. Cloning and chemical characterization of this gene will allow early diagnosis and intervention before any damage is done.

Progress in hereditary hearing impairment in the last several years has been in syndromes of hearing impairment and dominant, x-linked and mitochondrial nonsyndromic hearing impairment. Success in identifying genes responsible for recessive nonsyndromic hearing impairment has been limited to isolated populations. However, in the United States, 80% of congenital or early acquired hearing impairment or deafness is nonsyndromic and recessively transmitted.

To understand recessive nonsyndromic hearing impairment better, the NIDCD has established a Hereditary Hearing Impairment Resource Registry and a consortium dedicated to expediting this research. The consortium encourages the sharing of molecular genetic and clinical data and is developing a database. With analysis of these data, finding genes responsible for hearing impairment will be accelerated.

In view of the difficulty in finding genes for recessive nonsyndromic hearing impairment, the intramural program is modifying its investigative approach under the leadership of the new Director of Intramural Research, the distinguished molecular biologist and physician, James F. Battey, Jr. The traditional approach of using linkage analysis in searching for a gene does not always lead directly to cloning of the gene because the number of individuals in a family is so small. However, using a mouse mutant model has the advantage of generating hundreds of meioses from a single set of parents eliminating the problem of genetic heterozygosity inherent in human linkage studies. Complementing human studies by using animal models offers a systematic way to search for these genes in unisolated populations.

I am pleased to report on the development of an advanced, state-of-the-art modem that will accept both TTY and standard modem calls and that will benefit men, women and children who are hard of hearing, deaf, or speech impaired. This modem was developed through an NIDCD-supported small business innovation research grant and is impressive in its speed, accessibility through both Windows ™ and DOS software, and TTY/answering machine capability. Called the NexCom 300 ™, it has successfully made the transfer to the commercial market and is currently available for installation. Its developers are also looking into voice generation as a possible upgrade to the device. As the next step, they are working on the development of a "pen computer" TTY that will allow convenient access to a variety of telephone systems.

An NIDCD-supported investigator is examining the epidemiology of hearing impairment and hearing aid use in Americans who are Cuban-, Mexican- and Puerto Rican-Americans. Using the Hispanic Health and Nutrition Survey, the scientist is studying the prevalence of hearing impairment in children, developing a risk-factor profile of hearing-impaired adults and children and determining what encourages or impedes the use of hearing aids in Hispanic populations.

NIDCD is intensifying efforts to develop vaccines against otitis media. Middle-ear infections are the major cause of visits to emergency rooms and physicians' offices for young children. The pneumococcus and the nontypeable Haemophilus influenzae are two major pathogens that cause otitis media. Stage I and II clinical trials of vaccines against the pneumococcus are underway. The unsolved problem is selection of a candidate antigen for a vaccine against nontypeable Haemophilus influenzae. NIDCD intramural scientists are accelerating efforts to utilize a lipooligosaccharide (LOS)-derived oligosaccharide as the antigen. LOS is an endotoxin and a major surface antigen of nontypeable Haemophilus influenzae, and antibodies against it kill the bacterium. The strategy includes conjugating LOS with a protein, as was done with the Haemophilus influenzae type b vaccine against meningitis, so that the vaccine produces immunity in young infants.

Part of the NIDCD mission is to support efforts to create devices which compensate for lost and impaired sensory or communication functions such as cochlear implants and hearing aids. Profound hearing impairment often results from loss of the sensory hair cells of the inner ear due to injury or disease, and the sensory cells can be bypassed by the cochlear implant to stimulate the auditory nerve directly. Since the first cochlear implants in the 1960s, more than 14,000 adults and children have been implanted with these devices. The NIDCD has made major investments in the research and development of multichannel state-of-the-art cochlear implants. Critical to effective use of the cochlear implants has been the development of their speech processors. The NIDCD is supporting improved speech processors that are capable of extracting elements of speech and converting them into electrical signals at high speed. The result is not the same as what we would hear under normal circumstances, but it is perceptable as sound, and with training, understandable as speech. The NIH sponsored a consensus development conference on cochlear implants in 1988. In 1990, cochlear implants were approved by the FDA for use in children. New scientific and ethical issues have emerged since that first conference that must be addressed and therefore, on May 15th to 17th, 1995, the NIH is sponsoring a Consensus Development Conference on Cochlear Implants in Adults and Children.

The NIDCD and the Department of Veterans Affairs (VA) have established a multifaceted collaboration for hearing aid research and development. This collaboration is designed to improve hearing aids for 5 million current users of hearing aids and for an additional 10 million Americans who could benefit from them. The NIDCD has issued program announcements for research grant proposals on improving how hearing aids affect speech understanding in quiet and noise and how to evaluate the benefits of hearing aids. A contract for device development, like the ones that have been so successful in cochlear implant research and development, has recently been awarded. The first of a series of clinical trials will be initiated this year and will address the most fundamental hearing aid issues. It will also identify which strategies and technologies will benefit which subgroups of hearing-impaired men and women and under what circumstances. The NIDCD and the VA are also cosponsoring the first national hearing aid research and development conference in Bethesda in September of this year. We are pleased to be cooperating with the VA on establishing multicenter clinical trials and are convinced that this federal collaboration will be both cost and time effective in addressing the daily needs of millions of Americans, many of whom are in the senior decades of their lives.

Study of the chemical senses, the senses of smell and taste, has yielded important progress in several diseases. The misdiagnosis of progressive supranuclear palsy (PSP) as Parkinson's disease can have serious medical consequences. The two diseases have similar symptoms and signs. When NIDCD researchers found that PSP patients were able to perform well on smell identification tests but that Parkinson's patients performed poorly, they had found not only what may be helpful in diagnosing PSP but may be useful in early detection of Parkinson's. Further, contemporary imaging and molecular biological techniques applied to biopsies of olfactory sensory tissue may prove useful in the early diagnosis of Alzheimer's diseases. The olfactory neurons in Alzheimer's disease are the only affected neural tissue that can be easily obtained for study from living patients. The molecular pathogenesis of Alzheimer's disease is being diligently pursued by NIDCD scientists.

Another example of clinical progress is the reduction of mouth pain in cancer patients. Those of us who have known individuals who have undergone cancer chemotherapy and radiation therapy, are familiar with the extremely painful and debilitating sores in the mouth and esophagus experienced by them. This pain is demoralizing as it affects speaking, swallowing, nutritional status, and quality of life. NIDCD scientists working to alleviate these side effects of needed therapy combined capsaicin, the hot ingredient in chile peppers, with taffy. This capsaicin-laced candy reduces oral pain for these individuals for several hours at a time.

Preliminary results from studies of young children who suffered a unilateral brain injury, usually due to stroke before six months of age, suggest that the brain regions responsible for language learning in children are not necessarily the regions responsible for language maintenance and use in adults. Unlike adult aphasics, many of these children, although seriously delayed at first, will go on to display patterns of language comprehension and production like those of other children.

I am delighted to report the progress of the collaboration between the NIH Office of Research on Minority Health and the NIDCD called The Partnership Program. The Partnership Program provides students, faculty and administrators who are minoritiy individuals with opportunities in basic and clinical research in human communication in the labs of the the NIDCD as well as enhanced curriculum and training opportunities at their home institution. The participating academic centers for this new NIDCD initiative are: Morehouse School of Medicine/Atlanta University Complex, University of Puerto Rico School of Medicine/University of Puerto Rico, University of Alaska System, and Gallaudet University. Students in the partnership program have already reported results of their research conducted at the NIH at the NIDCD Research Festival and at their home medical institutions. The success of this demonstration program has resulted from the close cooperation between the staff of participating institutions and the NIDCD staff. An evaluation mechanism has been in place since the beginning, and the results will be shared with the NIH leadership.

In an attempt to stimulate more clinical trials in diseases affecting human communication, NIDCD recently solicited the interest of organizations having the capability and resources to design clinical trials cooperative groups that could plan, implement and conduct high priority therapeutic research. These groups would develop clinical trial protocols, and each protocol would be peer reviewed prior to commencement. The response to the request was tremendous and included professional and scientific organizations, medical centers and university consortia. The NIDCD plans to issue a request for applications for clinical trials cooperative groups in the spring of this year.

The NIDCD extramural and intramural research agenda capitalizes on scientific opportunities and a research momentum that is considered to be a high priority for the American public. Recently, NIDCD has appointed a blue-ribbon panel of extramural scientists to review the staff's analysis of the extramural and intramural research portfolios to determine how the NIDCD might better meet the opportunities in research in human communication.

The needs of 46 million Americans are constantly before us. So many of the conditions they are challenged by are chronically disabling and disheartening. Their disorders come at high cost to their families and to society. We have the leads to so many solutions. We have the scientific talent. We now have the tools of molecular biology, molecular genetics, informatics and imaging. We must exploit these leads to address the causes, the prevention, amelioration and management of many diseases and disorders of the most human of attributes . . . human communication.

The FY 1996 budget request is $172,399,000. Thank you for your consideration. I will be happy to answer any questions.

JAMES B. SNOW, JR., M.D.

Director
National Institute on Deafness and Other Communication Disorders
National Institutes of Health

Born: March 12, 1932, Oklahoma City, Oklahoma

Marital Status: Married, three children

Education: B.S., University of Oklahoma, Norman, Oklahoma, 1949-52; M.D., Harvard Medical School, Boston, Massachusetts, 1952-56

Professional History: Intern in Surgery, Johns Hopkins Hospital, Baltimore, MD, 1956-57; Resident in Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, 1957-60; Captain, Consultant in Otolaryngology; U.S. Army Medical Corps, 8th U.S. Army, 121st Evacuation Hospital, Korea, 1960-61; Otolaryngologist, U.S. Army Hospital, Fort Leonard Wood, MO, 1961-62; Assistant Professor and Vice-Chairman, Department of Otorhinolaryngology, University of Oklahoma Medical Center, Oklahoma City, OK, 1962-64; Professor and Head, Department of Otorhinolaryngology, University of Oklahoma Medical Center, Oklahoma City, OK, 1964-72; Professor and Chairman, Department of Otorhinolaryngology and Human Communication, University of Pennsylvania, School of Medicine, Philadelphia, PA, 1972-90; Director, National Institute on Deafness and Other Communication Disorders, Bethesda, MD, 1990-.

Society Affiliations: Alpha Omega Alpha; American Academy of Facial, Plastic and Reconstructive Surgery; American Academy of Otolaryngology-Head and Neck Surgery; American Association for the Advancement of Science; American Broncho-Esophagological Association; American College of Surgeons; American Laryngological Association; American Laryngological, Rhinological and Otological Society; American Medical Association; American Neurotology Society; American Otological Society; American Society for Head and Neck Surgery; American Speech-Language Hearing Association; Association for Research in Otolaryngology; Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum; International Bronchoesophagological Society; Johns Hopkins Medical and Surgical Association; Massachusetts Eye and Ear Infirmary Alumni Association; National Association of the Deaf; New York Academy of Sciences; Pan American Association of Otorhinolaryngology and Broncho-Esophagology; Phi Beta Kappa; Sigma Xi; Society for Ear, Nose and Throat Advances in Children; Society of University Otolaryngologists-Head and Neck Surgeons.

Honors and Awards: Regent's Award for Superior Teaching, University of Oklahoma, 1970; Certificate of Award, American Academy of Ophthalmology and Otolaryngology, 1971; Honorary Master of Arts, University of Pennsylvania, 1973; Second Vice-President, American Academy of Ophthalmology and Otolaryngology, 1973-74; Consulting Professor, Shanghai Second University of Medical Sciences, Shanghai, People's Republic of China, 1985; Honorary Fellow, Japan Broncho-Esophagological Society, 1985; Golden Award of the International Federation of Oto-Rhino-Laryngological Societies, 1989; Society of Scholars, Johns Hopkins University, 1991; Honorary Member, Association of Otolaryngologists of India, 1992; Distinguished Achievement Award, Deafness Research Foundation, 1993; Presidential Citation, American Otological Society, 1994.

OLFACTORY RESEARCH

Mr. PORTER. Thank you, Dr. Snow.

Could you expand on the comment that you made relating to nerve tissue in the nose and its use in the early diagnosis of Alzheimer's disease? How does that work and how have you come to this discovery?

Dr. SNOW. First let me say that one of the earliest findings in Alzheimer's disease is a loss of sensitivity of the sense of smell. And because of this demonstration of the loss of sensitivity, as an early sign in Alzheimer's disease, there's been a great deal of interest in studying the olfactory neuroepithelium in the roof of the nose.

All of the olfactory system is preferentially affected in Alzheimer's disease. Some of the earliest findings in Alzheimer's disease occur in the olfactory neuroepithelium, the olfactory bulb and the areas of the olfactory cortex. And so some have even postulated that the causative agent or an etiologic factor may enter the brain through the nose, through the olfactory system. And so there's been a great deal of interest in that.

One step in that direction was to develop a technique for biopsying the olfactory neuroepithelium, that is the tissue, the very thin tissue, that is right at the roof of the nose, right under the brain. It is possible to recover that tissue, it's possible to culture it, to culture the neurons.

You know, one of the characteristics of that kind of neural tissue is its ability to regenerate. It is constantly being reconstituted throughout the lifetime. Approximately every 30 days, our olfactory neurons are replaced. This is a very dynamic system. It is an important one as far as studying neural regeneration and transplantation of neurons. So there is this great interest in studying the pathologic changes that occur in these neurons and the tissue that surrounds them in Alzheimer's disease.

REVIEW OF THE RESEARCH PROGRAM

Mr. PORTER. Dr. Snow, your statement describes a blue ribbon panel of outside experts who have been asked to review your staff's analysis of your intramural and extramural research portfolio. What opportunities and modifications has the panel identified?

Dr. SNOW. The first meeting of the panel will occur on April the 6th. We have had a telephone conference with them to orient them to the meeting. We have provided them with the analysis. But it will be on April the 6th that we will get their reaction to our portfolio. We trust that they are diligently analyzing it according to their own expertise, and will come to that meeting with some ideas to be expressed. And it's only a one-day meeting. But considering the intellect of the individuals that have been selected for it and the format of the meeting, I think we will be able to get out of that some very valuable advice.

HEARING IMPAIRMENT

Mr. PORTER. Can you review for us the size of the hearing impaired population, both those who are profoundly deaf and those whose impairment is less severe?

Dr. SNOW. Yes. The very latest information is that there are 20.5 million people in the United States that have hearing trouble. This result is in the just-published report on the 1990 and 1991 National Center for Health Statistics interview survey.

Now, we know that in interview surveys, there is always an underestimation of hearing loss. So this 20.5 is probably not an exact figure. But it's a very useful figure. The Institute has consistently used 28 million as the number of hearing impaired Americans. And when 20.5 million are picked up by an interview, that 28 million is probably correct.

Now, in this latest data, 4.8 million people have difficulty understanding speech. Their hearing problem is so severe. So I think that may also be somewhat of an underestimate. But that is more than we had thought. There are various estimates as to how many individuals are truly deaf. That ranges from a half million people in the United States to 2 million. I believe that the 2 million is a more accurate estimate. And I think that the 4.8 million that have difficulty understanding speech tends to corroborate the higher estimate.

The other interesting statistic that came out of this that was a surprise to me and to many others is that 18.5 million people in the United States have tinnitus, have some sort of ringing, buzzing or sound in their ear. And many had underestimated that. This, I believe, is the first time that a question about tinnitus had been included in one of these interview surveys.

TINNITUS

Mr. PORTER. I have a question about tinnitus, so let me ask that. You indicate your research progress in the field has been limited by the relatively small number of scientists who have chosen this field.

Dr. SNOW. Yes.

Mr. PORTER. How do you plan to stimulate research into this disease?

Dr. SNOW. We have actually convened a meeting, a workshop that takes place tomorrow at the NIH, bringing in distinguished investigators who have worked in the field of tinnitus or in other areas of the hearing field, which might contribute to the development of new knowledge in tinnitus, to see what they would advise in the way of new strategies to be pursued. Also, there will be an international symposium on tinnitus this summer in July, in Portland, Oregon. We will be attending that to see what new ideas come out of that.

Tinnitus can occur anywhere in the auditory system. It can occur in the ear canal, it can occur with an abnormality in the middle ear, in the inner ear, in the nerve of hearing or anywhere in the central auditory pathways. So really all of the research that is done in the hearing program in the Institute may shed light on one form of tinnitus or another. It isn't a single problem. It's really most often a symptom of a disorder of the auditory system. And the other symptom, of course, is a loss of hearing. Usually, tinnitus and hearing loss are associated. So virtually any of the research that we do in the hearing program may contribute important information to understanding one form or another of tinnitus.

HAIR CELL REGENERATION

Mr. PORTER. Some have predicted that by the end of the century, trials will be conducted in humans on the regeneration of cochlear hair cells. Do you think this is a feasible time frame?

Dr. SNOW. Well, the end of the century is only four or five years off. And we're making great progress. We have literally monthly progress in hair cell regeneration. The experimentation, of course, is all at the animal level. We're trying to refine the information about which growth factors and other chemicals are most effective in stimulating regeneration of the auditory and vestibular hair cells. We can be hopeful that something can occur in the next four to five years that can be applied clinically. Looking at the problem in the perspective of the usual history, it will probably take longer than that.

Mr. PORTER. Is this therapy the answer to deafness for a large share of the population currently afflicted?

Dr. SNOW. Yes. The vast majority of the people that have hearing impairment have it on the basis of a loss of hair cells in the inner ear. And therefore, some way of stimulating their regeneration would be very helpful.

We've already learned a lot about the regeneration of hair cells. We now know what cells are the progenitor cells. We know how they migrate once they have begun to reproduce. We know the pattern that they take. We know about the innervation. We know that they become functional again, that they actually function in hearing. And so we have a lot of information that would indicate that this could very well be a practical application.

COCHLEAR IMPLANTS

Mr. PORTER. What about cochlear implants? What are the limitations and successes of these kinds of devices, and what share of the deaf population could ultimately be helped by implants?

Dr. SNOW. A great deal of progress has been made in cochlear implants. The individual who is born with hearing and develops speech and language and then in time loses their hearing, who has a cochlear implant, is greatly benefitted by the cochlear implant. Likewise, children who are born deaf and whose families choose for their special education to be of the oral, auditory form, benefit from the implantation of a cochlear implant at two to three years of age.

Individuals who have been born deaf and who have matured in the deaf culture, and I'm really saying that this takes place by age 13 or 14, beyond that age, those individuals do not benefit from a cochlear implant. If they receive a cochlear implant, they tend not to use it.

And so it is not something that can be applied for the half million to 2 million people that I've spoken of. But for the 4,000 children that come along each year with either congenital or early acquired deafness, it is an option, not the only option, but it is an option. And for those individuals who develop a loss of hearing later in life, it's a Godsend.

Mr. PORTER. Speaking about lifestyle or culture, there was an article in the New York Times Magazine last August that talked about the movement within the deaf community to celebrate deafness as an alternative lifestyle. This group does not necessarily want to have their deafness corrected. Have you faced any challenges to your work in deafness research because of this viewpoint?

Dr. SNOW. We're well acquainted with that concept from advice that we have received from individuals in the deaf community. One of the things that we did early on, after the formation of the Institute, was to have a working group, where representatives of the deaf community came to the Institute and advised us as to what kind of research they would like to have performed by the Institute.

This was not research for a cure or for a prevention or for treatment, but rather to allow them to communicate better, either deaf to deaf person or communication between a deaf person and a hearing person. And there is great pride in the deaf community, as well there should be, because of the great accomplishments that have occurred in that culture. And many individuals in the deaf community feel that adaptation with deafness, rather than an attempt to change the situation, is the high road. And we respect that, and agree with that.

Mr. PORTER. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. Chairman, at the outset, I want to associate myself with your comments regarding the service of Dr. Moskowitz. I've had the pleasure and the privilege over a number of years to have worked personally with him on matters in which I had a special interest at the Institute.

I want to join with Chairman Porter in not only commending you for the service you've given to the National Institutes of Health but also to this nation. And, I certainly want to wish you all the best in your new responsibilities at Wake Forest. It's been a pleasure to know you.

Dr. MOSKOWITZ. Thank you, Mr. Stokes. I too, have found it personally rewarding to work with you in our joint efforts. Especially in seeking and getting your advice in the development of programs to ensure that all Americans receive the proper health care and increase their quality of life, and furthermore to provide opportunities for all Americans to participate in a biomedical enterprise. And I congratulate you on your efforts.

Mr. STOKES. Thank you very much, Dr. Moskowitz.

Dr. Snow, it's nice to have this opportunity to talk with you.

Dr. SNOW. Thank you, sir.

OTITIS MEDIA

Mr. STOKES. Let me ask you, how extensive are middle ear infections in children and in adults?

Dr. SNOW. They are the most common localized infection in children. They are the greatest cause for visits to emergency rooms and to physicians' offices. In the Indian Health Service, otitis media is the most important reason patients visit for treatment. This is particularly true in the first five years of life. Otitis media first begins to appear during the latter part of the first year of life. It has its highest incidence during the second and third year of life. And then begins to decrease after five years of age.

This is a problem that is worldwide. It is the largest cause of acquired hearing impairment. And in adults, it also occurs, but it is far less frequent. It is not what I would consider a major public health problem in adults. For the individual who has otitis media and has the pain of the earache and the disability of the loss of hearing in that ear, it's a very serious problem. But it can ordinarily be successfully treated in the adult and doesn't represent the same kind of public health problem that it does in the child.

Mr. STOKES. So then, with a child, if the infection is either untreated or treatments is delayed, the possibilities of hearing impairment are even much more severe, is that what you're saying?

Dr. SNOW. Yes. And even when there is appropriate treatment for otitis media, it is often followed by a middle-ear effusion that lasts for weeks or months that either requires additional antibiotic therapy or surgery, such as myringotomy and insertion of a tympanotomy tube. The hearing loss that goes along with the middle-ear effusion has developmental consequences as well as consequences in educational attainment and in speech and language development.

Mr. STOKES. Do we know the causes of these infections?

Dr. SNOW. Yes. Although they are often started with a viral infection, as a common cold, very soon one of several bacteria take over and are thought of as the real cause. Its treatment needs to be directed to either the pneumococcus or the Haemophilus influenza or the Moraxelle catarrhalis or occasionally the streptococcus. And so if we could prevent those bacterial infections, and the two major ones are the pneumococcus and the Haemophilus influenzae, the non typeable Haemophilus influenzae.

HEARING IMPAIRMENT RESOURCE REGISTRY

Mr. STOKES. Doctor, how extensively is the Institute's hereditary hearing impairments resource registry expected to be used, and tell us what makes this registry unique?

Dr. SNOW. This registry is very important, because it serves the families that have hearing impairment. It gives them the opportunity to participate in genetic research if they'd like to do so. It is important to the biomedical research community, because it gives a collection of families that have similar forms of hearing impairment that could be studied genetically.

This is a national registry. Although it has been funded now for nearly two years, it has only recently received the OMB approval of the registration form, which is in a way a questionnaire. And now this is being distributed widely, and physicians and audiologists who might come in contact with individuals with a hearing impairment or families that have hearing impairment are being encouraged to acquaint families with this resource. If the families are interested in participating in genetic research, they may contact the registry which is located at the Boys Town National Research Hospital in Omaha, Nebraska.

GENETIC RESEARCH

Mr. STOKES. Doctor, you mentioned genetics. Is hereditary hearing impairment a real problem? Is that something that we know a great deal about?

Dr. SNOW. Yes. We've already found the genes for 40 or more different forms of hearing impairment. We've made the greatest progress in syndromes of hearing impairment, where there is some other features, some other finding, other than the hearing loss, so that the individual can be easily identified and recognized as having a hereditary disorder.

We've also made considerable progress in finding the genes for dominant, sex-linked and mitochondrial genes that cause nonsyndromic hearing impairment. The big problem, of course, is that there are many individuals that have recessive nonsyndromic hearing impairment. These are the ones that represent 80 percent of the congenital and early onset hearing impairment in the United States. And these are the individuals we would like very much to register.

But looking at hearing impairment more broadly, virtually all hearing impairment is either genetically determined or there is a predisposition that is on a genetic basis. For example, we now know that aminoglycoside antibiotic ototoxicity has at least in some families a genetic predisposition. Asian families have been identified, individual families both from Japan and from China, who have an unusual susceptibility to aminoglycoside antibiotics. Although this environmental factor is required, the aminoglycoside antibiotic, the genetic predisposition is required for the hearing loss to occur, when only the usual dosage of the drug has been utilized.

Just as we have found this genetic predisposition to aminoglycoside ototoxicity, we also believe that there is a genetic predisposition to noise-induced hearing loss. And indeed, I believe that there is a genetic determination for presbyacusis, the hearing loss that is associated with aging.

If you take all of those together, then we're talking about the vast majority of all hearing impairment. And that's why we emphasize the molecular genetics of hearing impairment to such a very great extent at the NIDCD.

Mr. STOKES. You mentioned antibiotics. Recently the media has been giving increased attention to the excess use of antibiotics. Does extensive use of antibiotics for treatment of ear infections create a problem for the average person suffering from frequent ear infections?

Dr. SNOW. Yes, sir, in the sense that the pneumococcus is becoming resistant to antibiotics. The pneumococcus used to be exquisitely sensitive to penicillin, and was no problem to treat. It was one of the ideal organisms to treat. Now there are resistant forms of the pneumococcus that are appearing in otitis media, pneumonia and other rather common infections. And where in the past it was no problem to treat those, it is now a problem.

This is a further reason why we must have a vaccine against the pneumococcus that is not just effective in older children and adults, but is also effective in the first few months of infancy. Determining the efficacy of this vaccine is what the stage I and II clinical trials are doing. And that's what we're aiming for in developing the nontypeable H. influenzae vaccine against otitis media. That will be a vaccine that will be given in the first few months of life, just like the Haemophilus influenzae type B vaccine against meningitis is given in the first few months of life. It's achieving that immunogenicity in the first few months of life that is the technical problem.

HEARING AID RESEARCH

Mr. STOKES. Doctor, how widely used are hearing aids?

Dr. SNOW. We have characteristically said that there are 5 million hearing aids in use in the United States. The publication that I referred to earlier from the 1990–91 survey says that it's more like 3.6 million hearing aids in the United States. Probably that's an underestimate and the 5 million figure is probably not wrong. And we believe that another 15 million people in the United States could benefit from a hearing aid. They either don't have one because of the cost involved or because the current hearing aids don't meet their needs very satisfactorily.

Mr. STOKES. Doctor, last month the subcommittee had the opportunity to hear testimony from a number of this Nation's Nobel laureates. About seven or eight of them sat at the same table where all of you are seated. And they gave us some extremely important insight, particularly with reference to the status of the Nation's biomedical research enterprise. They indicated to us that neurological research is one of the most important areas that if enhanced, offered considerable opportunity to further medical advances. To what extent is this area of research a high priority area of investment for your Institute?

Dr. SNOW. This represents a very high priority for us. About $90,000,000 of our budget is spent on one form of neuroscience or the other. Since we're dealing with four, five if you count touch, sensory systems, and because we're dealing with the output portion of the communication system in terms of voice, speech and language, virtually everything that we deal with is neuroscience. It's a very important part of our work.

Mr. STOKES. How much is included in your fiscal year 1996 budget request for this area?

Dr. SNOW. For neuroscience?

Mr. STOKES. Neuroscience.

Dr. SNOW. I don't have a——

Mr. STOKES. Well, you can provide it for the record.

Dr. SNOW [continuing]. Specific figure for that. Well, I'm sorry, I do, sir. The estimate is $86,315,000.

Mr. STOKES. And how does that compare, Doctor, with your fiscal year 1995 and 1994?

Dr. SNOW. In 1994, it was $81,311,00. And in 1995, it was $83,800,000.

CLINICAL TRIALS

Mr. STOKES. Doctor, clinical trials are the backbone for bringing basic research and advances in medical treatments. NIH supported clinical trials have yielded significant health benefits for the American people. And, they have yielded comparable economic savings. Can you tell us what are the four most significant clinical trials that are currently underway at your Institute, and what are the expected benefits to be achieved?

Dr. SNOW. Well, certainly one of the most important areas of clinical trials for us are cochlear implants. These are not just one trial, but there are several going on, involving both children and adults. The outcome of these studies are to determine which individuals will benefit from which form of cochlear implant and under what circumstances. We have such clinical trials at the University of Iowa. We have them at the Harvard Medical School, at Indiana University, and so I think that would be probably one of the most important.

Next I would probably put emphasis on the early identification of hearing impairment, the clinical trial to determine the very best way of identifying which infants have a hearing impairment and which do not. And it's important, of course, to do this within the first several months of birth.

As you recall, we had a Consensus Development Conference in 1993, and that panel, that consensus panel, recommended for the first time anywhere in the world that universal screening of infant hearing be accomplished within the first three months of life. They were a little ahead of us in that we still need to develop the information as exactly what is the best way to do that.

We think that a combination of measuring otacoustic emissions and auditory brain stem responses is the most effective way. We believe that the answer will come out of this clinical trial.

Another area of great importance is the neurogenic communication disorders, the injuries to the brain or to the nerves to the vocal cords that produce interference with voice, speech and language. And that clinical trial is of great importance.

And then we have several, for the fourth I would choose clinical trials in aphasia. This is the loss of speech following stroke. And we have a couple of clinical trials in that area. We are interested in stroke, not only in the elderly, but stroke also occurs during the first year of life. And the effect on language of the loss of blood supply to portions of the brain in the first year of life is also of great importance to us.

And so I guess I would consider cochlear implants, the early identification of hearing impairment, neurogenic communication disorders and aphasia the main ones, the most important.

MINORITY RESEARCH

Mr. STOKES. Doctor, let me ask you this. Over the past few weeks, as we've had the head of each of the different Institutes appear here, almost invariably they have talked to us about a disparity in the health care between the majority population and African Americans and/or other minorities. I would be interested in knowing if your Institute is doing any special type of research in this area as it relates to minorities?

Dr. SNOW. Yes. We are in a number of areas. One of the important areas is in cytomegalovirus infections. These are congenital infections that occur in utero and cause approximately one fourth of the acquired hearing impairment in children. There is a disproportionately larger percentage of African Americans that suffer from these infections as compared to the majority population.

Our investigators have developed a diagnostic test of the saliva that is quicker and less expensive than the old test, where the virus had to be cultured from the urine. That was expensive and prolonged before one got the answer.

So we have a special interest in these viral infections and are supporting several investigators studying not only the diagnosis and the natural history of the illness, but have also developed an animal model of congenital infection with this virus.

We are in the process of trying to develop a collaboration with the Indian Health Service on the study of the epidemiology of otitis media in Native American children. It has long been thought that this was a special problem for Native American children. The last major study was carried out in 1978, and we think it is time to do this now.

One of the important considerations in this study are new risk factors, such as prone sleeping versus sleeping on the back. What's been found, because of the interest in sleep position, because of sudden infant death syndrome, and as you know, there's a Public Health Service campaign to encourage parents to put their children down to sleep on their back, in studying these children is that there is less otitis media with sleeping on the back as compared to sleeping prone.

And we also have some tentative evidence that the hearing outcome is better in infants who are put on their back to sleep. This is a topic that we would like to study in this particular population that has a high prevalence of otitis media, along with other risk factors, such as passive smoking, indoor wood stoves, the sleeping arrangements in the home, and the amount of day care; all of these are factors that disproportionately affect minority infants and children.

Mr. STOKES. Thank you, Dr. Snow. It's been a pleasure to listen to you. Thank you very much.

Dr. SNOW. Thank you, Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

HEARING AID RESEARCH

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Snow, your budget justification indicates that the contract program for identifying new types of hearing aids will begin soon. What new approaches are you targeting, and does miniaturization hold promise?

Dr. SNOW. Yes. There are a number of new strategies that are being studied through the grants that have been awarded. The smaller a hearing aid is made and the closer that it is placed toward the tympanic membrane, toward the ear drum, the better. This leads to less of the adverse side effects of a hearing aid, such as the feedback and the occlusive effect that is like having one's head in a barrel, and to better the speech understanding. So there has been a move to move the hearing aid into the ear canal and to approach the tympanic membrane as close as possible. Ultimately, of course, hearing aids may be implanted into the middle ear. This would be a step even farther.

There is a great interest in multiple microphones for the pickup of sound for hearing aids. There is evidence that that is a good way to reduce the interference from background noise. In digital hearing aids, and programmable hearing aids progress is being made.

Mr. PORTER. So you would not say that technological developments are lagging in the hearing aid field?

Dr. SNOW. No, they're moving along. The trouble is that we don't know when we come to an individual what hearing aid to prescribe for that individual. And the purpose of the clinical trial that you mentioned is to find out what subset of the hearing-impaired population does best with a given strategy or a given technology. We think that there are subsets within the hearing-impaired population that will do better with some than with others. And we're starting out with what ought to have been done years ago of examining the more basic forms of technology to see which subgroups of the hearing impaired population do best with those.

This starts a series of clinical trials that will be of great value to hearing impaired people as we sort out these problems. And each subsequent trial can be built on the information that we have gained from the previous trial.

PARTNERSHIP PROGRAM

Mr. PORTER. Dr. Snow, what kind of interaction does NIDCD have with Gallaudet University?

Dr. SNOW. We have a formal collaboration with Gallaudet. Several of our grants go to faculty members at Gallaudet University. We have a formal collaboration in the Partnership program. As you know, the NIDCD has developed a partnership with four academic centers to provide research training opportunities for minority individuals who have been underrepresented in basic and clinical research. We have included among those academic institutions Gallaudet University. And that represents an exchange program where their students, graduate students, postdoctoral students, and indeed their faculty can come to the NIDCD, to our laboratories in Bethesda for periods of training.

Likewise, their administrators can come to our extramural program to learn more about the granting process. And it is an opportunity for us to help them with the development of their curriculum in certain areas and to facilitate their research on their own campus in those areas of expertise of the NIDCD.

Mr. PORTER. Dr. Snow, thank you very much for the fine job you're doing at NIDCD, and for your testimony today, which was also a very fine job. Thank you very much for being here. And Dr. Moskowitz, we again wish you well.

The subcommittee is in recess until tomorrow at 10:00 a.m.

[The following questions were submitted to be answered for the record:]

SPECIAL EMPHASIS AREAS

Mr. Porter: Provide a table identifying the 1994-1996 spending on the following: hearing aid development, otitis media vaccine, Meniere's disease, stuttering, noise-induced hearing loss, tinnitus, and dystonia?

Dr. Snow: Special Emphasis Areas:
(Dollars in Thousands)

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
Hearing Aid Development	$8,227	$10,291	$10,642
Otitis Media Vaccine	311	348	375
Meniere's Disease	583	589	611
Stuttering	1,111	1,149	1,188
Noise-Induced Hearing Loss	4,530	4,596	4,761
Tinnitus	90,080	93,141	96,320
Spasmodic Dysphonia	339	380	407

CLINICAL TRIALS COOPERATIVE GROUP

Mr. Porter: Explain for us the concept behind your clinical trials cooperative groups.

Dr. Snow: The National Institute on Deafness and Other Communication Disorders (NIDCD) is inviting applications from organizations, institutions, or consortia of institutions that have the capability and resources to organize multicenter cooperative clinical trials of the efficacy of treatment for diseases and disorders of human communication. These consortia, referred to as Cooperative Groups, will plan, implement, conduct, analyze and disseminate results of clinical trials on the treatment or management of diseases and disorders of hearing, balance, smell, taste, voice, speech or language, or any combination thereof.

The Cooperative Group must be able to quickly transform a new research concept into an active protocol, complete the protocol within a specified time period, analyze and publish the results in peer-review publications for the benefit of the entire scientific community, integrate findings with current research, and develop subsequent research concepts. The Cooperative Group will identify key unanswered questions substantiating the need for clinical trials in human communication, and formulate scientific agendas prioritized according to public health need for approval by the NIDCD; secure support for patient care and related costs to enable the proposed trials to run to completion; provide administrative, data management, and statistical support for the planning, implementation, execution, analysis and dissemination of the results of the clinical trials; provide onsite monitoring of safety and quality assurance; and establish and administer a separate Data and Safety Monitoring Committee for each clinical trial, responsible for monitoring progress of the clinical trial, performance of clinical facilities, the safety of the participants, and the efficacy of treatments being tested.

Mr. Porter: Is there a pipeline of research ready to be tested in trials, or would these groups start from scratch, producing the basic research and then testing it?

Dr.Snow: Yes, there is a pipeline of research ready to be tested. The primary goal is to evaluate existing and new therapeutic strategies and interventions, based upon emerging knowledge of the biological and other factors influencing disease development and progression and treatment outcome. This initiative is specifically designed to strengthen the coordination of the NIDCD research agenda with progress in basic research and to emphasize the rapid utilization of these discoveries in mulitidisciplinary clinical research.

Mr. Porter: Would the groups represent specialty areas or would they test a wide range of approaches?

Dr. Snow: A wide range of approaches will be tested. The objective is to provide support for clinical trials collaborative groups proposing to access the appropriate at-risk populations and to provide the expertise to construct and conduct controlled clinical trials addressing issues in the treatment of diseases and disorders affecting hearing, balance, smell, taste, voice, speech, or language.

Mr. Porter: Is this mechanism used broadly throughout the NIH?

Dr. Snow: This mechanism is used by the National Cancer Institute and perhaps others. Nevertheless, it will require innovative and creative approaches for application to the disorders of human communication. The NIDCD is confident that this mechanism is appropriate for initiating a research program in clinical trials by providing a support infrastructure for such endeavors.

RESEARCH ADVANCEMENTS

Mr. Dickey: What recent advancements have been made regarding deafness?

Dr. Snow: Our understanding of deafness has been enhanced through recent NIDCD investigations from a number of perspectives. Using molecular genetic information obtained from an Indonesian family with nonsyndromic hereditary hearing impairment who live in an isolated village, scientists have been able to map a gene to the same region on chromosome 1 for an American family with a similar pattern of inherited hearing impairment. The different ethnic backgrounds and geographic separation of the two families suggest that this gene may be responsible for hearing impairment in other populations throughout the world.

An NIDCD-supported group of investigators has developed a sensitive and specific saliva test for cytomegalovirus (CMV) that can be used for newborn infants. Congenital CMV infection is known to be a leading cause of sensorineural hearing loss (SNHL) in young children. Since most infected neonates appear normal at birth, newborn screening for CMV infection has relied on the culture of the virus from urine. Because this procedure is expensive and slow and not easily instituted on a universal basis, an inexpensive and rapid method of screening for CMV infection was needed to explore the potential role of CMV in SNHL in young children.

NIDCD-funded scientists have made important progress in the ototoxicity caused by aminoglycoside antibiotics. Although is has been known that certain aminoglycoside can be ototoxic (can induce deafness), detecting who might be susceptible to this occurrence has been difficult. The discovery that in some cases susceptibility to aminoglycoside ototoxicity can be transmitted through the maternal line equally to both genders was used to predict the involvement of mitochondrial genes since all the mitochondria in an individual are maternal in origin. Current work has revealed at least one common defect in the mitochondrial genome in unrelated Asian families with multigenerational instances of aminoglycoside-induced deafness.

An NIDCD-funded research group has recently mapped the gene for Crouzon syndrome to a small area on chromosome 10. Crouzon syndrome is a relatively common hereditary developmental defect, which is characterized by abnormalities of the head and neck and hearing impairment.

Tools for infant hearing screening are being improved by the development of a compact device for testing of auditory brain stem responses.

NIDCD scientists funded through the Small Business Innovation Research program have also made progress in alleviating ringing "feedback," a common complaint of many hearing aid users.

Clinical results obtained from children with cochlear implants suggest that one of the most important factors contributing to the differences in performance is the length of time that they have used the device. If their hearing loss is prelingual, children with implants develop speech perception skills over a long course of time, learning continues in children who have used an implant for as long as five years. Related results show that the ability to understand speech by cochlear implant users continues to improve even after four or more years of multichannel cochlear implant use.

NOISE-INDUCED HEARING LOSS

Mr. Dickey: To what extent is deafness brought on by certain behaviors, such as not wearing hearing protection?

Dr. Snow: Exposure to loud noise has long been recognized as the cause of a major form of hearing impairment, noise-induced hearing loss. Noise-induced hearing loss can be prevented by wearing hearing protectors such as plastic ear plugs and ear muffs filled with glycerine. Unfortunately, many individuals are not aware of the danger of excessively loud sounds and of the need for hearing protection. They may engage in risky behavior in the workplace or in recreational activities without hearing protection. The proper use of hearing protection, whether in an occupational or recreational setting, is highly effective.

Mr. Dickey: What specific behaviors have been identified that increase or decrease the incidence of deafness?

Dr. Snow: Allowing oneself to be exposed to loud noise without hearing protection is a specific behavior that can increase the incidence of hearing impairment. It is estimated that over 20 million Americans are regularly exposed to hazardous noise. Exposure to intense noise can occur in many occupations. Other specific behaviors that place the hearing at risk from intense noise are firing small arms, using machines powered by internal combustion engines such as lawnmowers, using wood working equipment such as power and chain saws, and riding snowmobiles without wearing hearing protectors.

GENETIC RESEARCH

Mr. Dickey: What other types of deafness occur independent of specific behaviors?

Dr. Snow: Hearing impairment and deafness may occur on a genetic basis, result from infections and trauma, be induced by ototoxic drugs such as guinine, result from immunototoxic disorders and aging.

FETAL HEARING DEVELOPMENT

Mr. Dickey: What research has been done to study fetal hearing and communication development?

Dr. Snow: Three naturally occurring acoustic stimuli are continuously available to the developing fetus. These are maternal voice, heart sounds and bowel sounds. These naturally occurring sounds are functionally important for the newborn. For example, maternal heart sounds have been used in neonatal intensive care nurseries to calm premature infants. Studies have also shown that on the first day of life, human newborns exhibit a preference for their mother's voice compared to that of another woman.

Scientists have studied fetal response to external acoustical stimulation delivered via speakers placed on the maternal abdomen. Fetuses have been shown to "startle" to pure tones at or above 100 decibels (dB) at seven months gestation. Near term fetuses have been shown to react to airborne pure tones above 100 dB with heart rate acceleration. With pure tones between 85 to 100 dB, the same fetuses exhibit heart rate decelerations.

Other research has shown that near term fetuses stimulated by vowel sounds delivered through a loud speaker placed over the maternal abdomen also have changes in heart rate. Under the proper experimental conditions, near term fetuses have been shown to discriminate between different vowel sounds.

In addition, when presented with different categories of stimuli to which the fetus had been systematically exposed during the last weeks of gestation, without any other postnatal exposure except during testing, newborns (2 to 4 days old) show preferences for previously experienced stimuli including: (a) specific musical sequences; (b) specific speech sequences; and (c) specific language of the mother. Such preferences imply underlying fetal auditory discrimination ability.

HEARING IMPAIRMENT IN THE AGING

Mr. Dickey: To what extent do hearing disorders occur among older Americans, as opposed to children or infants?

Dr. Snow: The number of hearing-impaired people in the United States is expected to increase substantially in the next few decades due to increasing longevity and the consequent overall aging of the population. By far, the largest group of Americans suffering from hearing loss are the elderly. Thirty to 35 percent of the United States population between the ages of 65 to 75 years have a hearing loss severe enough to require a hearing aid. Presbycusis, the hearing loss accompanying aging, increases with age, so that 40% over the age of 75 years would benefit from amplification. Presbycusis affects both the ability to hear sounds as well as the ability to understand speech.

OTITIS MEDIA

Mr. Stokes: How extensive are middle ear infections in children and in adults?

Dr. Snow: Otitis media is the single most frequent reason for a child to make a sick visit to a pediatrician's office besides the common cold in the United States. It is estimated that otitis media accounted for 31 million of the 130 million office visits for respiratory diseases from 1986-1989. Seventy-six percent of children will have experienced otitis media by their sixth birthday. The highest incidence of otitis media occurs in the six to eleven month age group. Many children have recurrent episodes of this disease. Some sources estimate the cost in terms of missed school days, medications, and missed parent's workdays, etc. to be in excess of 3 billion dollars a year. Otitis media is a much more significant health problem in children than adults, but it should be noted that it does occur in adults and is a source of significant discomfort in these patients.

Mr. Stokes: If left untreated or if treatment is delayed, what are the implications?

Dr. Snow: If otitis media is left untreated, a chronic effusion, or fluid, can develop in the middle ear resulting in hearing impairment which can adversely affect the child's development, particularly of verbal skills, and educational progress during a highly critical period of development. Recently, it was found that sentence recognition was adversely affected among children with a history of otitis media with effusions in both ears. Several prospective studies have documented the short- and long-term effects of otitis on language development, showing a substantive inhibition of language development in children with an early and long history of otitis media.

In addition, it is well established that untreated otitis media can progress to labyrinthitis resulting in sensorineural hearing loss, or meningitis which is particularly devastating in children under one year of age, with all the destructive sequelae that accompany this potentially life-threatening disorder.

Mr. Stokes: Do we know what causes these infections and are there collaborative efforts underway between your Institute, the NIAID, and the NICHD to accelerate the development of a vaccine for this health problem?

Dr. Snow: Otitis media is caused primarily by three bacterial pathogens: *Streptococcus pneumoniae,* (33%), nontypeable *Haemophilus influenzae* (21%), and *Moraxella catarrhalis* (14%). There is a widespread recognition of the need for an effective vaccine for infectious diseases, including otitis media, caused by pneumococci. Numerous groups, including leading pharmaceutical manufacturers (Praxis Biologics, Merck, Sharp & Dome, and Connaught), are actively pursuing this objective and a few have entered phase I/II clinical trials.

Less attention is being paid to a vaccine directed against nontypeable *Haemophilus*. For this reason, we have chosen to direct our efforts in this direction, in an effort to complement and not duplicate efforts already underway in the private sector. Our goal is to generate a vaccine that confers protective immunity against this pathogen within the first year of life. We will model our efforts based on the very successful vaccine development directed against *Haemophilus influenzae* type b, where the complex sugar on the bacterial outer surface was conjugated to a protein carrier, resulting in a conjugate vaccine that gave protective immunity in young children. For the nontypeable *Haemophilus* vaccine, we are planning to use detoxified endotoxin (lipooligosaccharides) obtained from this organism conjugated to a protein carrier as a vaccine candidate.

Our vaccine effort is an active collaboration among the Vaccine Unit of Laboratory of Cellular Biology, DIR, NIDCD, NIH, the Laboratory of Developmental and Molecular Immunity, DIR, NICHD, NIH, and the Laboratory of Bacterial Polysaccharide, Division of Bacterial Products, Center for Biologics and Evaluation, FDA. Human resources needed to execute this project are jointly share by all institutes, and material resources are largely supported by NIDCD.

Mr. Stokes: How much is included in the FY 1996 budget request for research in this area, and how does it compare with the funding level for FY 1995 and 1994?

Dr. Snow: The vaccine initiative is a relatively new effort, which was initiated during FY 1993. We estimate that we have dedicated about $311,000 in FY 1994 and $348,000 in FY 1995 to preliminary efforts in this area. So far, these efforts appear to be progressing very well, and we project a major expansion in this area in FY 1996. The budget for this unit in FY 1996 will be about $375,000, with additional expansion planned in future years if the venture continues to fulfill its promise.

SBIR-SUPPORTED RESEARCH

Mr. Stokes: According the opening statement, researchers have developed and transferred to the commercial market an advanced, state-of-the-art modem that will benefit individuals who are hard of hearing, deaf, or speech impaired. How affordable is this advice? What was the cost from research to market and what is the projected cost benefit of this device?

Dr. Snow: This device was initially supported by a Phase I SBIR grant, establishing its technical merit and feasibility. Following Phase I support, the grant was awarded support for Phase II, continuing the research or research and development efforts initiated in Phase I. To date, this grant has received $550,000 from the NIDCD. Because it is still in its development stage, and has therefore not gone to market, we are not able to project its affordability, total cost from research to market or its cost benefit.

Mr. Stokes: How extensively used is the small business innovation research grant and the CRADA funding mechanisms by your institute?

Dr. Snow: The NIDCD supported 20 SBIR awards for $2,704,000 in FY 1994. The Institute does not support any CRADAs at this time.

HEARING AID RESEARCH

Mr. Stokes: How widely used are hearing aids, and to what extent have technological advances been applied to improving hearing aids?

Dr. Snow: There is a significant portion of the hearing-impaired population whose hearing loss would make them appropriate for hearing aid usage, yet they choose not to use hearing aids. While over 25 million Americans suffer from some degree of hearing impairment, only about 20% of that number have hearing aids. The problem of background noise is probably the most often cited reason for user dissatisfaction and is also one of the most technically challenging problems facing scientists who are participating in hearing aid research and development. Technological advances currently under investigation with applications towards improving hearing aids include a) multi-microphone, directional microphone and microphone array technology designed to enhance the reception of speech by reducing interference from background noise, b) new signal processing strategies involving multiband gain control, amplitude compression and techniques for reducing the effects of background noise, c) the development of headset hearing aids using multimicrophone technology and d) determination of the best ways to manipulate speech signals in order to enhance speech understanding when using a hearing aid.

NEUROSCIENCE RESEARCH

Mr. Stokes: Last month, the committee had the opportunity to hear testimony from the nation's Nobel Laureates. We welcomed the insight they provided on the status of the nation's biomedical research enterprise. They indicated that neurological research was one of the most important areas that if enhanced--offered considerable opportunity to further medical advances. To what extent is this area of research a high priority investment for your Institute?

Dr. Snow: Neuroscience research has been and continues to be a high priority investment area for the National Institute on Deafness and Other Communication Disorders. This research includes spectacular advances recently made in such areas as the regeneration of sensory receptors of hearing, balance and olfaction, hereditary hearing impairment, and the biochemistry and pharmacology of central taste pathways and of the auditory and vestibular systems. Further progress in these areas cannot fail to lead to dramatic advances in the prevention and treatment of disorders of hearing and balance, and in the treatment of disorders of smell and taste. Disorders of the sense of smell are, for example, very common in the elderly and are associated with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.

Mr. Stokes: What opportunities are ready to be exploited and what are the potential benefits?

Dr. Snow: Scientific opportunities calling for early exploitation include rapidly expanding understanding of the phenomenon of sensory cell regeneration and our growing capability to identify the genes responsible for hereditary hearing impairment. Each of these factors will lead to more effective management of hearing impairment. In the case of cell regeneration it will be possible to stimulate regeneration of hair cells within the inner ear which have been damaged by noise exposure or ototoxic medications, thus restoring hearing; in hereditary hearing impairment it will be possible to replace a defective gene thus preventing or treating some varieties of inherited hearing impairment.

Mr. Stokes: How much is included in the FY 1996 budget request for this area of research?

Dr. Snow: The FY 1996 estimate for neuroscience research is $86,315,000.

Mr. Stokes: How does it compare with FY 1995 and FY 1994?

Dr. Snow: In FY 1994, we obligated $81,311,000 for neuroscience research, and estimate $83,758,000 for FY 1995.

CLINICAL TRIALS

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously?

Dr. Snow: The National Institute on Deafness and Other Communication Disorders is actively encouraging applications for the support of clinical trials of new or existing but controversial treatment modalities, and of innovative modifications of existing therapies in the areas of human communication. Recognizing the importance of the early entry of the findings of such clinical studies into clinical practice, applicants seeking support for this type of research are being asked to ensure prompt publication of the findings of trials. Continued funding of clinical trials will be contingent upon compliance with this policy.

Mr. Stokes: Is there a specific system in place for disseminating such information, explain?

Dr. Snow: The National Institues of Health (NIH) has set guidelines for alerting physicians and the public about clinical trial findings in cases in which timely and broad dissemination of results could prevent morbidity and mortality. Timely and thorough information on research results should assist physicians in recommending, advising against, or offering treatment.

PARTNERSHIP PROGRAM

Mr. Stokes: I understand that the Institute has a new partnership program underway with minority institutions, can you share your progress with the committee?

Dr. Snow: Through a memorandum of understanding between the NIDCD and the Office of Research on Minority Health, the NIDCD Partnership Program presents unique opportunities for underrepresented minorities to participate in fundamental and clinical research in human communication. The participating academic centers are the Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, the University of Puerto Rico, and Gallaudet University. Each academic center has developed objectives relative to the intent of the program and their specific needs. These objectives include: establishment of symposia, career fairs and curriculum revisions in the areas of hearing, balance, smell, taste, voice, speech and language; expansion of research and training efforts involving human communication; and recruitment of high school, undergraduate, graduate and medical students to careers in human communication.

Students from the Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, and the University of Puerto Rico have already participated in the program. Student research results were presented at the NIDCD Research Festival and at the University of Puerto Rico Medical School.

Students who are deaf or hard of hearing are being supported in this program as they are also currently underrepresented in biomedical and behavioral research.

SUCCESS RATES

Mr. Stokes: The total number of research grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the congressional justification, the NIH's FY 1996 Budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, what has happened to your Institute's success rate over the past five to ten to fifteen years, explain?

Dr. Snow: The NIDCD has been in existence from 1989. From FY 1989 to FY 1994 the number of research project grants has increased steadily from 286 in 1989 to 490 in 1994.

In 1989 the success rate was 38.2%, and it dropped to 32% in 1994.

RPG AVERAGE COSTS

Mr. Stokes: What has been the trend in the average cost of research project grants over the same time period? What is the trend in constant dollars?

Dr. Snow: The following data identifies the average cost of research project grants in real and constant dollars. The trend in the average cost of research project grants has risen from $181,468 in 1989 to $184,850 in 1994.

1989		1994	
Real	Constant	Real	Constant
$181,468	$181,468	$184,850	$146,642

SUCCESS RATES

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Snow: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. Both in FY 1989 and FY 1994, over a third of NIDCD applicants chose not to answer the optional questions, which makes it especially difficult to draw any conclusions about success rates in most minority categories. The following table lists success rates in five-ear increments, beginning in FY 1989 for self-identified minority scientists, however, since there is no way to predict the composition of over a third of the applicants, the data may not provide a true representation of NIDCD's support of minority scientists.

Competing Grant Success Rates for Minority Scientists
In Five-Year Increments FY 1989, and FY 1994
NIDCD

Fiscal Year /Race	Asian	African American	Hispanic	Native American	Unknown*	White
1989	25.0%	NA	33.3%	NA	37.5%	32.7%
1994	27.6%	33.3%	NA	NA	35.7%	31.4%

* May include minority scientists who chose not to answer optional questions related to race/ gender.

Mr. Stokes: What is the success rate for research applications received from women researchers?

Dr. Snow: The following table lists success rates for women applicants who chose to answer the optional questions on the grant application related to race and gender. The category denoted as "unknown" represents applicants whose gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIDCD's support of women scientists:

Competing Grant Success Rates for Women Scientists
In Five-Year Increments FY 1989, and FY 1994
NIDCD

Fiscal Year /Gender	1989	1994
Female	33.3%	36.7%
Unknown*	37.5%	35.7%

* May include women scientists who chose not to answer optional questions related to gender.

Mr. Stokes: What is the success rate for research applications received from African American researchers?

Dr. Snow: The following table lists success rates for African-American applicants who chose to answer the optional questions on the grant application related to race. The category denoted as "unknown" represents applicants whose race could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIDCD's support of African-American scientists.

Competing Grant Success Rates for African-American Scientists
In Five-Year Increments FY 1989, and FY 1994
NIDCD

Fiscal Year /Race	1989	1994
African-American	NA	33.3%
Unknown*	37.5%	35.7%

* May include African-American scientists who chose not to answer optional questions related to race.

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Snow: The NIDCD has not received any research project applications from any of the historically black colleges. Therefore, a success rate cannot be determined.

RPG AVERAGE COSTS

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to minority researchers?

Dr. Snow: As previously stated, questions related to race and gender are identified as optional on all NIH research grant applications. Both in FY 1989 and FY 1994, over one-third of NIDCD applicants chose not to answer the optional questions, which makes it especially difficult to draw any conclusions about average costs in most minority categories. The following table lists average costs in five-year increments, beginning in FY 1989 for self-identified minority researchers, however, since there is no way to predict the composition of over one third of the applicants, the data may not provide a true representation of NIDCD's support of minority scientists.

Competing Grant Average Costs for Minority Scientists
in Real and Constant Dollars
In Five-Year Increments FY 1989, and FY 1994
NIDCD
(Dollars in thousands)

	FY 1989		FY 1994	
	Real	Constant	Real	Constant
Asian	$224.3	$224.3	$117.4	$ 93.1
African-American	NA	NA	115.7	91.8
Hispanic	139.7	139.7	NA	NA
Native American	NA	NA	NA	NA
Unknown*	391.5	391.5	216.5	171.7
White	171.8	171.8	176.9	140.3

* May include minority scientists who chose not to answer optional questions related to race/ gender.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to women researchers?

Dr. Snow: The following table lists the average cost of competing awards to women researchers in real and constant dollars. The category denoted as "unknown" represents applicants whose gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIDCD's support of women researchers:

Competing Grant Average Costs for Women Scientists
in Real and Constant Dollars
In Five-Year Increments FY 1989, and FY 1994
NIDCD
(Dollars in thousands)

	FY 1989		FY 1994	
	Real	Constant	Real	Constant
Women	$118.4	$118.4	$160.3	$149.5
Unknown*	391.5	391.5	216.5	171.7

* May include women scientists who chose not to answer the optional questions related to gender.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to African-American researchers?

Dr. Snow: The following table lists the average cost of competing awards to African-American scientists in real and constant dollars. The category denoted as "unknown" represents applicants whose race could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NIDCD's support of African-American scientists:

Competing Grant Average Costs for African-American Scientists
in Real and Constant Dollars
In Five-Year Increments FY 1989, and FY 1994
NIDCD
(Dollars in thousands)

	FY 1989		FY 1994	
	Real	Constant	Real	Constant
African American	NA	NA	$115.7	$91.8
Unknown*	391.5	391.5	216.5	171.7

* May include African-American scientists who chose not to answer the optional questions related to gender.

Mr. Stokes: What is the average cost for research applications received from HBCUs?

Dr. Snow: The NIDCD does not support grants at HBCUs at this time.

MINORITY SUPPORT

Mr. Stokes: According to a November 1993 article appearing in the Chronicle of Higher Education, White scholars received 90 percent of the research grants awarded competitively by the National Institutes of Health in 1991. The study found that in the same fiscal year, Asians had received about 8 percent of such grants, Hispanics 1.5 percent, and African Americans 0.4 percent. What are the current statistics for Institute?

Dr. Snow: To comply with Federal mandates, questions related to race and gender are identified as optional on all NIH research grant applications. As a result, the NIDCD is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. In 1994 over one third of the NIDCD grant applicants choose not to complete the portion of the grant application referring to race and gender and are coded "unknown." Thus the data may not accurately represent NIDCD's support of minority scientists. For 1994:

White	65 percent
Asians	5 percent
African Americans	1 percent
Hispanics	NA percent
Unknown*	29 percent

* May include minority scientists who chose not to answer the optional questions related to gender.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

FY 1996 Budget — Page No.

Organization chart 196

Appropriation language 197

Amounts available for obligation 199

Budget mechanism table 200

Summary of changes 202

Budget authority by object 204

Administrative costs 206

Significant items in House Appropriations Committee report 207

Authorizing legislation 209

Appropriation history 210

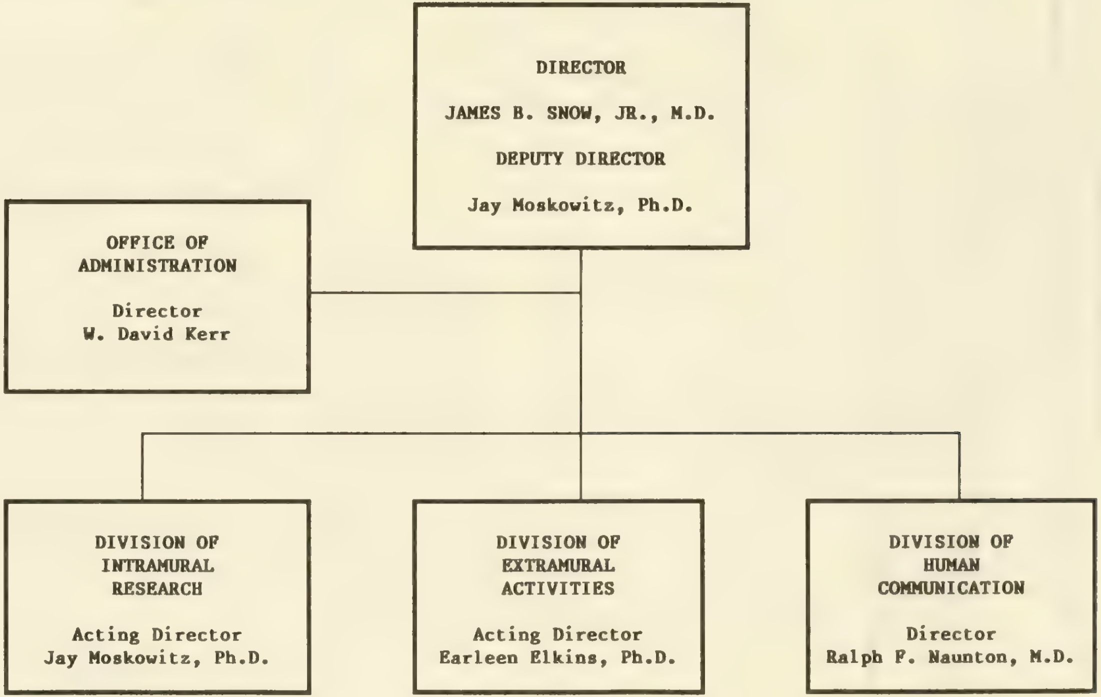
Budget authority by activity 211

Justification:

A. General statement 213
B. Extramural research 215
C. Intramural research 222
D. Research management and support 225
E. Detail of full-time equivalent employment (FTE) 227
F. Detail of end-of-year employment 228

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS



NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to deafness and other communication disorders, [$166,886,000] $172,399,000.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation................	$162,823,000	$166,886,000	$172,399,000
Section 205 Procurement reduction..................	---	-69,000	---
Section 207 Rental reduction..	---	-9,000	---
Section 513 S&E reduction.....	---	-47,000	---
Subtotal, adjusted appropriation...........	162,823,000	166,761,000	172,399,000
Comparative transfer to: Office of AIDS Research for HIV activities............	-849,000	---	---
Comparative transfer from: Office of the Director for two positions.............	223,000	215,000	---
Comparative transfer from: Other NIH Institutes for Management Fund adjustment	516,000	405,000	---
Subtotal, adjusted budget authority..............	162,713,000	167,381,000	172,399,000
Unobligated balance, lapsing..	-41,000	---	---
Total obligations...........	162,672,000	167,381,000	172,399,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994--$2,798,000; FY 1995--$3,500,000; FY 1996--$3,500,000.

Also excludes funding for HIV activities: FY 1995--$1,552,000; FY 1996--$1,650,000, included in Office of AIDS Research, NIH.

Note: Excludes $22,316 in FY 1994 and $25,125 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting	388	$81,275,000	382	$81,616,000	383	$85,462,000
Administrative supplementals	(18)	286,000	(16)	266,000	(16)	274,000
Competing projects:						
Renewals	63	15,394,000	60	15,266,000	58	15,460,000
New	91	13,098,000	86	12,989,000	84	13,153,000
Supplements	1	119,000	1	119,000	1	121,000
Subtotal, competing	155	28,611,000	147	28,374,000	143	28,734,000
Subtotal, research projects	543	110,172,000	529	110,256,000	526	114,470,000
Total, SBIR/STTR	20	2,704,000	20	3,069,000	21	3,139,000
Total, RPGs	563	112,876,000	549	113,325,000	547	117,609,000
Research Centers:						
Specialized/comprehensive centers	14	16,011,000	16	17,070,000	16	17,050,000
Other Research:						
Research career programs	40	3,101,000	43	3,697,000	43	3,676,000
Cooperative clinical	1	1,330,000	1	1,027,000	1	1,025,000
Minority biomedical support	0	105,000	0	575,000	0	586,000
Other research	14	589,000	15	719,000	15	733,000
Subtotal, other research	55	5,125,000	59	6,018,000	59	6,020,000
Total, research grants	632	134,012,000	624	136,413,000	622	140,679,000

Research Training:						
Individual awards:						
Noncompeting	15	427,000	25	700,000	25	728,000
Competing awards	18	444,000	8	203,000	8	203,000
Subtotal, individual	33	871,000	33	903,000	33	931,000
Institutional awards:						
Noncompeting	139	3,871,000	155	4,363,000	155	4,446,000
Competing awards	31	639,000	15	311,000	15	312,000
Subtotal, institutional	170	4,510,000	170	4,674,000	170	4,758,000
Total, research training	203	5,381,000	203	5,577,000	203	5,689,000
Research and development contracts	14	5,813,000	15	6,532,000	15	6,590,000
	FTEs		FTEs		FTEs	
Intramural research	45	9,967,000	43	11,023,000	43	11,468,000
Research management and support	80	7,540,000	71	7,836,000	70	7,973,000
Total	125	162,713,000	114	167,381,000	113	172,399,000
Clinical trials		(6,177,000)		(7,691,000)		(7,792,000)

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Summary of Changes

1995 Estimated budget authority	$167,381,000
1996 Estimated budget authority	172,399,000
Net Change	+5,018,000

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural:				
a. Within grade increase	---	$3,997,000	---	+$37,000
b. One more day of pay	---	3,997,000	---	+15,000
c. Annualization of January 1995 pay increases	---	3,997,000	---	+20,000
d. 1996 pay increases	---	3,997,000	---	+87,000
e. Payment for centrally furnished services	---	1,217,000	---	+62,000
f. Increased cost of service and supply fund	---	477,000	---	+24,000
g. Increased cost of materials and other supplies	---	5,809,000	---	+140,000
Subtotal				+385,000
2. Research Management & Support:				
a. Within grade increase	---	4,599,000	---	+65,000
b. One more day of pay	---	4,599,000	---	+18,000
c. Annualization of January 1995 pay increases	---	4,599,000	---	+23,000
d. 1996 pay increases	---	4,599,000	---	+78,000
e. Unemployment compensation	---	4,599,000	---	+1,000
f. Payment for centrally furnished services	---	1,791,000	---	+69,000
g. Increased cost of service and supply fund	---	245,000	---	+14,000
h. Increased cost of materials and other supplies	---	1,446,000	---	+33,000
Subtotal				+301,000

Summary of Changes--Continued

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting............	382	$81,882,000	+1	+$3,854,000
b. Competing................	147	28,374,000	-4	+360,000
c. SBIR/STTR................	20	3,069,000	+1	+70,000
Subtotal, RPGs...........				+4,284,000
2. Research centers............	16	17,070,000	--	-20,000
3. Other research				
a. Research career awards...	43	3,697,000	--	-21,000
b. Cooperative clinical.....	1	1,027,000	--	-2,000
c. Minority biomedical research supplement....	--	575,000	--	+11,000
d. Other research...........	15	719,000	--	+14,000
4. Research training				
a. Individual awards........	33	903,000	--	+28,000
b. Institutional awards.....	170	4,674,000	--	+84,000
5. Research and development contracts..................	15	6,532,000	--	+58,000
Subtotal, Extramural.....				+4,436,000
	FTEs		FTEs	
6. Intramural research..........	43	11,023,000	--	+60,000
7. Research management and support....................	71	7,836,000	-1	-164,000
Total Changes.........				+5,018,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	114	113	-1
Full-time equivalent of overtime and holiday hours	.1	.1	---
Average SES salary	$111,282	$113,507	---
Average GM/GS grade	10	10	---
Average GM/GS salary	$44,168	$45,051	+$883
Average salary of ungraded positions	20,923	21,258	+335
Personnel Compensation:			
Full-time permanent	$4,348,000	$4,312,000	-$36,000
Other than full-time permanent	1,395,000	1,488,000	+93,000
Other personnel compensation	170,000	183,000	+13,000
Special personnel services	1,264,000	1,395,000	+131,000
Total personnel compensation	7,177,000	7,378,000	+201,000
Personnel benefits	1,414,000	1,461,000	+47,000
Benefits to former personnel	5,000	6,000	+1,000
Travel and transportation of persons	334,000	357,000	+23,000
Transportation of things	39,000	47,000	+8,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Rental payments to others...........	$500,000	$548,000	+$48,000
Communications, utilities and miscellaneous charges.............	587,000	640,000	+53,000
Printing and reproduction...........	72,000	80,000	+8,000
Other services:			
Consultant services............	80,000	117,000	+37,000
Other services.................	2,613,000	2,868,000	+255,000
Purchases from Govt. accounts..	3,531,000	3,270,000	-261,000
Operation of GOCOs.............	---	---	---
Research and Development Contracts....................	6,532,000	6,590,000	+58,000
Supplies and materials..............	957,000	1,018,000	+61,000
Equipment...........................	1,550,000	1,651,000	+101,000
Grants, subsidies & contributions...	141,990,000	146,368,000	+4,378,000
Total, budget authority........	167,381,000	172,399,000	+5,018,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time Permanent (11.1)............	$4,348,000	$4,312,000	-$36,000
Other than Full-time Permanent (11.3)..	1,395,000	1,488,000	+93,000
Other Personnel Compensation (11.5)....	170,000	183,000	+13,000
Special Personnel Services (11.8)......	1,264,000	1,395,000	+131,000
Total Personnel Compensation (11.9)..	7,177,000	7,378,000	+201,000
Civilian Personnel Benefits (12.1).......	1,414,000	1,461,000	+47,000
Benefits to Former Personnel (13.0)......	5,000	6,000	+1,000
Travel (21.0)..........................	334,000	357,000	+23,000
Transportation of Things (22.0)..........	39,000	47,000	+8,000
Rental Payments to Others (23.2).........	500,000	548,000	+48,000
Communications, Utilities, and Miscellaneous Charges (23.3)...........	587,000	640,000	+53,000
Printing and Reproduction (24.0).........	72,000	80,000	+8,000
Consulting Services (25.1)..............	80,000	117,000	+37,000
Other Services (25.2)...................	2,613,000	2,868,000	+255,000
Purchases of Goods & Services from other Government Accounts (25.3)...	3,531,000	3,270,000	-261,000
Supplies and Materials (26.0)...........	957,000	1,018,000	+61,000
Total..............................	17,309,000	17,790,000	+481,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Significant Items in House Appropriations Committee Report

Item	Action Taken or to be Taken
1995 House Report	
Auditory Hair Loss	
The House in its report 103-553, page 60, stated: "The Committee is aware of recent advances in the understanding of the molecular events leading to auditory hair loss. The problem is a major cause of hearing loss both from exposure to intense noise and from toxic reactions to certain drugs. The Committee encourages furthur studies in this promising area of research.	The NIDCD will has a currently active program announcements soliciting investigator-initiated research applications focusing on the molecular bases of repair and regeneration of the auditory hair cell. Current research is focusing on the role of growth promotion substances in hair cell proliferation, incuding the regulation of hair cell gene activity.
Dystonia	
The House in its report 103-553, page 60, stated: "The Committee commends the Institute's recent progress on understanding this form of dystonia and recommends further NIDCD intramural and extramural study of the disorder.	Laryngeal dystonia, also known as spasmodic dysphonia, has been studied in the NIDCD intramural program since 1985. Ongoing research is determining these patients brain function abnormalities using neuroimaging, the pathophysiology producing laryngeal muscle spasms and the events proceeding the onset of symptoms. Immediate plans are to initiate studies of families with these voice disorders and to develop neural prostheses for patients not helped by botulinum toxin injection. The NIDCD currently supports a number of research projects

within the Voice and Speech Program that are related to the scientific area of dystoni It is anticipated and expectec that the Institute will contin to receive and fund applicatio that examine dystonia.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Funded Authorizations:						
Research and Investigation..........	Section 301	42§241	Indefinite	$161,804,000	Indefinite	$166,710,000
National Institute on Deafness and Other Communication Disorders	Section 464 A-F	42§281	Such sums as necessary		Such sums as necessary	
National Research Service Awards.........	Section 487(d)	42§288	Such sums as necessary	5,577,000	Such sums as necessary	5,689,000
Total Budget Authority				167,381,000		172,399,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1989 [2]	---	---	$87,600,000	$86,530,000
1990	$99,902,000	$99,952,000	121,116,000	118,839,000 [3]
1990 Sequester				-1,256,000
1991	122,847,000	125,623,000 [4]	148,247,000	134,935,000 [5]
1991 Sequester				-2,000
1992	146,321,000	144,495,000	151,106,000	149,102,000 [6]
1993	157,301,000	153,466,000	157,301,000	154,814,000 [7]
1994	153,088,000	162,823,000	162,823,000	162,823,000
1995 [8]	167,129,000	166,155,000	167,129,000	166,761,000
1996 [8]	172,399,000 [9]			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The House allowance excluded funds for the unauthorized training programs (National Research Service Awards). The Senate allowance includes the budget for NRSA's. It included up to $93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget of the NRSA program and provided up to $96,100,000 for the establishment of the proposed new institute, NIDCD.

3/ Excludes enacted administrative reductions of $161,000.

4/ Excludes $3,123,000 in NRSA training programs requested but not considered.

5/ Excludes the enacted administrative reduction of $3,562,000.

6/ Excludes the enacted administrative reduction of $1,041,000.

7/ Excludes the enacted administrative reduction of $1,528,000.

8/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

9/ Excludes enacted administrative reductions of $69,000, $9,000, and $47,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Deafness and Other Communications Disorders

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Deafness and Other Communication Disorders...	---	$132,748	---	$137,599	---	$145,165	---	$148,522	---	$152,958	---	+$4,436
Intramural research.........	38	8,168	44	9,223	45	9,967	43	11,023	43	11,468	---	+445
Research management and support..............	84	7,349	89	7,215	80	7,540	71	7,836	70	7,973	-1	+137
Total obligations.........	122	148,265	133	154,037	125	162,672	114	167,381	113	172,399	-1	+5,018
Unobligated balance lapsing..................	---	41	---	121	---	41	---	---	---	---	---	---
Total, budget authority.....	122	148,306	133	154,158	125	162,713	114	167,381	113	172,399	-1	+5,018

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute on Deafness and Other Communication Disorders

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
125	$162,713,000	114	$167,381,000	113	$172,399,000	-1	+$5,018,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute on Deafness and Other Communication Disorders. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Deafness and Other Communication Disorders (NIDCD) is responsible for conducting and supporting research in human communication.

Included in the program areas are research and research training on normal and disordered mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD is actively involved in health promotion and disease prevention.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

The President's appropriation request of $172,399,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NIDCD during the last five years has been as follows:

	Amount	FTEs
FY 1991	$134,476,000	97
FY 1992	148,306,000	122
FY 1993	154,158,000	133
FY 1994	162,713,000	125
FY 1995	167,381,000	114

Purpose and Method of Operation

Extramural research and training are supported through seven program areas: hearing, balance, smell, taste, voice, speech, and language. Funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at the NIH Clinical Center and laboratories at the Bethesda, Maryland campus. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

Overall Budget Policy

The FY 1996 budget request for the NIDCD is $172,399,000, an increase of $5,018,000 over the comparable FY 1995 level of $167,381,000.

The FY 1996 budget request for research project grants is $117,609,000, an increase of $4,284,000 or 4 percent over the FY 1995 estimate. The total number of research project grants to be awarded in FY 1996 is 547, compared to 549 in FY 1995. The request level will support 143 new and competing renewal research project grants at an average cost of $200,937. The request will support 383 noncompeting research project grants at an average cost of $223,138.

The NIDCD will support 16 research centers in FY 1996 at $17,050,000, a decrease of $20,000 from FY 1995.

Other research grants will total 59 for $6,020,000, a less than one percent decrease in funding from FY 1995.

An estimated 203 full-time training positions (FTTP) for $5,689,000 will be supported under the National Research Service Award program, which is the same number as FY 1995 and an increase in funding of $112,000.

The research and development contract budget of $6,590,000 will support 15 contracts, an increase of $58,000 over FY 1995.

The FY 1996 budget request for intramural research is $11,468,000, an increase of $445,000 over FY 1995.

The request for research management and support is $7,973,000, an increase of $137,000 over FY 1995. The FY 1996 request includes 113 FTEs, as compared to 114 in FY 1995.

National Institute on Deafness and Other Communication Disorders

Extramural Research

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$145,206,000	$148,522,000	$152,958,000	+$4,436,000

The NIDCD has primary responsibility at the National Institutes of Health for extramural research and research training in hearing, balance, smell, taste, voice, speech, and language.

Funding for the NIDCD extramural research program during the last five years has been as follows:

	Amount
FY 1991	$121,280,000
FY 1992	132,748,000
FY 1993	137,720,000
FY 1994	145,206,000
FY 1995	148,522,000

Rationale for the Budget Request

With the FY 1996 extramural request these funds will provide support for the following activity: Deafness and Other Communication Disorders program, $152,958,000, an increase of $4,436,000 over the FY 1995 estimate of $148,522,000.

Finding Genes for Hereditary Hearing Impairment

Most genetically transmitted hearing impairment occurs without other clinical signs and is therefore called "nonsyndromic." Using molecular genetic information obtained from an Indonesian family with nonsyndromic hereditary hearing impairment who live in an isolated village, scientists have been able to map a gene to the same region on chromosome 1 for an American family with a similar pattern of inherited hearing impairment. The different ethnic backgrounds and geographic separation of the two families suggest that this gene may be responsible for hearing impairment in other populations throughout the world.

PSP, Parkinson's and Alzheimer's

Errors in differentiating the diagnoses of individuals with various neurodegenerative diseases can have serious medical consequences. For example, progressive supranuclear palsy (PSP), a rare disease, is often misdiagnosed as the more prevalent Parkinson's disease because the two diseases share many motor symptoms and signs. Because PSP does not respond to medications for Parkinson's disease, the misdiagnosis can delay appropriate intervention. Research has revealed that testing of the sense of smell may be useful in the differential diagnosis of individuals in the early stages of PSP. PSP patients perform well on smell identification tests, whereas Parkinson's disease patients perform poorly. Further, the application of contemporary imaging and molecular biologic techniques to biopsies of olfactory sensory tissue may prove useful in the early diagnosis of brain diseases, such as Alzheimer's disease, in which the olfactory neurons are the only affected neural tissue that can be readily obtained from living patients.

Cochlear Implants

The cochlear implant is the first neural prosthesis to gain widespread clinical acceptance. Basic and clinical research involving these auditory prostheses are ongoing. Clinical results obtained from children with implants suggest that one of the most important factors contributing to the differences in performance is the length of time that they have used the device. If their hearing loss is prelingual, children with implants develop speech perception skills over a long course of time. In fact, this learning still occurs in children who have used an implant for as long as five years. Related results show that the ability to understand speech by cochlear implant users continues to improve even after four or more years of multichannel cochlear implant use. The NIDCD, in conjunction with the NIH Office of Medical Applications of Research, will be sponsoring a Consensus Development Conference on Cochlear Implants in Adults and Children in May of 1995, at the NIH in Bethesda, Maryland. This conference promises to review and evaluate the scientific issues concerning this technology and to provide a consensus statement that will be useful to health care providers and the public at large.

Advances for Deaf and Hard-of-Hearing Newborns and Adults

Tools for infant hearing screening are being improved by the development of a compact and rapid infant hearing screening instrument incorporating otoacoustic emission and auditory brainstem response testing.

NIDCD scientists funded through the Small Business Innovation Research program have made progress in alleviating ringing "feedback," a common complaint of many hearing aid users. By physically delivering sound deeper into the ear canal via improved hearing aid shell designs, hearing aid users experience less feedback and reduced occlusion effects. These occlusion effects, a common complaint of hearing aid users described as "hollowness" or a feeling of "talking inside a barrel," are also reduced. Other scientists are examining better ways to test hearing. For example, a prototype for a commercial software product developed for Spanish-speaking individuals is being altered to meet the growing demand for materials to test the hearing of children and adults whose first language is not English. These pilot projects show promise for the eventual commercialization of an important new product designed to benefit millions of hearing-impaired persons.

Maternal Transmission of Susceptibility to Antibiotic-induced Deafness

Inheritance patterns of disease often provide clues to the genetic basis of the disorder. While the proclivity of certain antibiotics to be ototoxic, or to induce deafness, has been recognized for many years, the detection of susceptible individuals has remained an enigma. The discovery that in some cases susceptibility to antibiotic-induced ototoxicity can be transmitted through the maternal line was used to predict involvement of mitochondrial genes. Mitochondria are intracellular structures which are involved in energy metabolism, and contain their own chromosome and genes. All the mitochondria in an individual are maternal in origin, since sperm do not contribute mitochondria to the egg during fertilization. Current work has revealed at least one common defect in the mitochondrial genome in unrelated Asian families with multigenerational instances of antibiotic-induced deafness. This work offers hope for a potential screening test to detect some individuals that are at risk for the development of antibiotic-induced deafness.

Tinnitus

An NIDCD-supported investigator is providing evidence that spontaneous otoacoustic emissions (SOAE), sounds that are produced by and emitted from the ear, may be a much greater contributor to the incidence of tinnitus than previously indicated. Measurement difficulties may have contributed to this underestimate. Further, there are data suggesting that some SOAEs may be produced by extrinsic factors and could serve as a source of environmentally induced tinnitus. Current research may provide further links between SOAEs and tinnitus by attempting to see if suppression of SOAEs will reduce the perception of tinnitus in some patients.

Progress in research on tinnitus, a symptom associated with many kinds of hearing loss, has been limited by the relatively small numbers of scientists who have chosen tinnitus as their area of research, as well as by the difficulties in ascertaining which auditory system mechanisms contribute to tinnitus. To address these problems, the NIDCD plans to hold a workshop on "Defining Future Directions for Tinnitus Research" in Fiscal Year 1995. The meeting will bring together scientists involved in tinnitus research with other investigators in related basic and clinical research areas that are pertinent to an understanding of the potential mechanisms that may contribute to this disorder. The goals of the meeting will be to define critical areas for future tinnitus research, and develop strategies for increasing the number of scientists addressing the complex issues related to tinnitus.

Mapping the Gene for Cruzon Syndrome

Cruzon syndrome is a relatively common hereditary developmental defect, characterized by abnormalities of the head and neck and hearing impairment. Until recently, genetic information was limited to knowledge that this syndrome was recessively transmitted--one copy of the gene must be inherited from each parent. A NIDCD-funded research group has recently mapped the gene for Cruzon syndrome to a small area on chromosome 10.

Cloning and structural analysis of this gene will allow its detection prenatally and in unaffected potential carriers and provide the foundation for gene therapy in affected individuals.

A New Screening Test for Cytomegalovirus Infection in Newborns

Congenital cytomegalovirus (CMV) infection is known to be a leading cause of sensorineural hearing loss (SNHL) in young children. Since most infected neonates appear normal at birth, newborn screening for CMV infection had relied on the culture of the virus from urine. This is a lengthy and expensive procedure, not easily instituted on a universal basis. As a result, the overwhelming majority of infected children go undetected. A rapid and inexpensive method of screening for CMV infection was needed to explore the potential role of CMV in SNHL in young children. A NIDCD-supported group of investigators has developed a sensitive and specific saliva test for CMV, which is applicable for the testing of newborn infants. This assay, combined with longitudinal testing for auditory deficits, will allow an assessment of the true prevalence of congenital CMV infection-induced SNHL in a large study population.

As further information is gained regarding the role of CMV infection as an important risk for childhood SNHL, the need for the development of a vaccine to prevent maternal CMV infections may become more urgent. An alternative approach to this problem could be the identification of antiviral agents to prevent hearing loss in infected newborns.

Reduction of Mouth Pain in Cancer Patients

Cancer chemotherapy and radiation therapy kills rapidly proliferating cells in mucous membranes. This cell death often causes the development of many painful sores in the mouth and esophagus during treatment. The pain experienced by patients receiving cancer therapy impairs speech, eating, nutritional status, and overall quality of life. Scientists have discovered that taffy candy combined with capsaicin, the active ingredient in chile peppers, reduces oral pain of these patients for several hours. Capsaicin is known to desensitize chemical pain fibers. The initial burn produced by capsaicin is reduced by sucrose and tactile stimulation, both of which are provided by the candy.

Portable Communication Device for Deaf and Speech-Impaired Individuals

A NIDCD SBIR grant has supported the development of a portable communication device that will soon be commercially available. The device will be of great use to individuals who are deaf or speech impaired. This exciting research effort is resulting in a "pen computer" TTY. TTYs are well suited as "deaf telephones" but are slow and incompatible with standard modems. This work has created new modem technology which will allow deaf and speech-impaired individuals to use standard high-speed modems and conveniently communicate via the telephone with standard modem systems and modem users. This will open up new opportunities for information access previously not available to these individuals. The new technology will appear in several different forms: one is an easy-to-carry pen computer TTY, which will provide the individual convenient TTY access to a variety of telephone systems.

Voice Disorders Associated with Parkinson's Disease

Of the 1.5 million individuals with the progressive neurogenic disorder Parkinson's disease, at least 89% have a breakdown in their ability to speak. The long-term goals of one study are to evaluate the efficacy of a model of behavioral voice treatment for these patients and to examine the physiologic and neural mechanisms underlying voice and speech changes that occur during treatment or with progression of the disease. Preliminary analysis indicates beneficial increases in movement of the vocal folds and improved stability of the voice accompanying treatment. To assess the underlying changes associated with successful treatment further, a number of patients with Parkinson's disease are being evaluated for variables in speech physiology such as vocal loudness, voice quality, and speech intelligibility. All of these measures improve significantly after treatment that focused on the voice. In most cases these post-treatment improvements were maintained for one to two years without additional treatment. After voice treatment, patients reported that they spoke more often and had more confidence because people could now understand them. These findings document that Parkinson's disease patients can make changes in their speech production in response to voice treatment; they also suggest that stimulating improved phonation may be a key to improving their overall speech production.

Literacy and Deaf Individuals

Deaf high school graduates on average read at a third to fifth grade level. Realization that phonological awareness and processing, that is, the ability to recognize and manipulate individual sounds in the spoken word are important in the development of reading and writing skills has led scientists to investigate these abilities in deaf individuals. Without complete auditory access to information about phonology, it might be expected that deaf students would be unable to use phonological processing and therefore that they would not become good readers. NIDCD researchers have shown that skilled deaf readers do use phonological coding. The possibility was explored that phonological awareness and processing, phonological awareness in particular, could be trained in beginning readers. Deaf children were exposed to phonological awareness training through a computer program which presented pictures for classification on the basis of beginning, middle, or ending sounds. Control groups received training in semantic classification using the same computer and pictures. Results indicate that deaf children improve in their phonological segmentation skills and in reading following phonology training. This did not occur following semantics training. These results support a link between phonological training and reading success in deaf children and their use in reading programs for deaf students.

Collaborative Effort to Improve Hearing Aids

The NIDCD continues an innovative collaboration with the Department of Veterans Affairs (VA) in an effort to support the development of better hearing aids. Five initiatives have been developed and are in various stages of implementation. These initiatives include a call to the research community for the submission of grant proposals to determine how hearing aids affect speech understanding, in quiet and in noise, published in January 1994. There was also a call for research to determine ways to measure the benefit received from hearing aids by hearing-impaired persons, also published in 1994. A contract for a program of device development for hearing aids will begin in the near future. This will support the design and evaluation of creative new technologies and strategies for hearing aids. The protocol for a first clinical trial has been developed and is expected to begin in Fiscal Year 1995 through an interagency agreement with the VA. The clinical trials will identify specific subgroups of individuals who benefit most from the existing and newly developed hearing aid technologies. A hearing aid research and development conference, scheduled for September 1995, will be a national forum for the presentation of research relevant to hearing aids. This collaborative effort between the NIDCD and the VA is facilitating progress toward the improved use of existing devices, as well as stimulating research to develop new technologies and devices.

Hearing Loss and Hearing Aid Use in Hispanic-Americans

A NIDCD-supported investigator is examining a number of issues related to hearing loss and hearing aid use in Americans of Cuban, Mexican, and Puerto Rican decent, using the Hispanic Health and Nutrition Survey (HHANES). Specific points being addressed are the prevalence of hearing impairments in children, development of a risk-factor profile of hearing-impaired adults and children, and determining factors which encourage or impede the use of hearing aids. This study will be invaluable in the development of programs to prevent and ameliorate hearing impairment in the Hispanic population.

Molecular Genetics of Communication Disorders

Velocardiofacial syndrome (VCFS) is an autosomal dominant disorder. Children with this disorder have a spectrum of abnormalities which include cleft palate, cardiac defects, facial anomalies, and speech and learning disabilities. There are several major goals of a newly funded NIDCD research project on VCFS. Scientists want to understand VCFS better by precisely defining the spectrum of its phenotype and genotype. They are developing molecular-diagnostic tests to identify patients with VCFS earlier than they are now diagnosed. Children with VCFS often receive treatment for cardiac emergencies without being identified as having VCFS. The majority of VCFS patients develop difficulties in speech and language, and it is these communication disorders which eventually bring them to the attention of clinicians who recognize that these children have VCFS.

The ability to identify patients with VCFS prior to the onset of speech development, prenatally or during the neonatal period, will allow earlier management of potential communication problems. This project exemplifies the contribution that molecular genetics can make to the amelioration of speech and language disorders.

Clinical Trials Cooperative Groups

The NIDCD has encouraged organizations having the capability and resources to organize clinical trials cooperative groups. These consortia would plan, implement, conduct, analyze and disseminate results of high priority clinical trial research in the treatment of diseases and disorders affecting hearing, balance, smell, taste, voice, speech and language. The Cooperative Group Steering Committee would select between five and seven hypotheses for which clinical trial protocols would be designed to answer high-priority questions in any of the seven mission areas of NIDCD. Each protocol will be peer reviewed prior to commencement of the grant.

Central Auditory Processing in Elderly People

Early diagnosis of certain dementias is now a being facilitated by a battery of central auditory tests with elderly patients. One disease known to cause deterioration of neuronal circuits is a form of Alzheimer's disease called "Mild Senile Dementia of the Alzheimer's type." These patients also suffer from hearing loss. Using an extensive audiologic testing battery, it was demonstrated that all measures of pure-tone hearing and recognition of simple words were similar between subjects with neurodegenerative disease and otherwise normal elderly subjects. However, when presented with complex sentence tests specifically designed to assess the processing capabilities of the higher level auditory structures, patients with mild neurodegenerative disease could not perform the test. Mild neurodegenerative diseases appear to affect central auditory processing and thus the ability to process more complex acoustic signals.

Childhood Focal Brain Injury and Subsequent Language Abilities

NIDCD investigators currently are studying children with focal brain injury (children who have suffered a unilateral brain injury, usually due to stroke, before six months of age). Results suggest that most (though not all) of these children eventually go on to display patterns of language comprehension and production that are indistinguishable from those who do not suffer such injury. However, many of these children are seriously delayed in the initial stages of language learning, suggesting that the injured cerebral hemispheres do not have the same potential for language as they did at birth and that a significant amount of reorganization must take place before language can be acquired. Furthermore, the correlations observed to date between patterns of language delay and lesion type are qualitatively and quantitatively different from the patterns observed in analogous studies with aphasic adults. Preliminary results suggest that the regions responsible for language learning in children are not necessarily the regions responsible for language maintenance and language use in adults.

Opportunities for Research in Molecular Pathology of the Ear

The NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry was established in September 1992. As a resource, the Registry enables investigators to locate all temporal bones and associated brain tissue specimens with a specific diagnosis in the United States.

With the recent development of techniques for antigen retrieval and DNA extraction from processed temporal bones, temporal bone collections are of great research value for the molecular characterization of the causes of disease in the auditory and vestibular systems.

National Institute on Deafness and Other Communication Disorders

Intramural Research Program

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
45	$9,967,000	43	$11,023,000	43	$11,468,000	--	+$445,000

The mission of the NIDCD Intramural Research Program is to conduct basic and clinical research on the normal processes and diseases and disorders of hearing, balance, smell, taste, voice, speech and language. These efforts range from basic multidisciplinary biological research to clinical trials of newly developed medical and surgical therapies. The Laboratories and Research Clinics are located at the NIH in Bethesda, Maryland.

Funding for the Intramural Research Program during the last five years has been as follows.

	Amount	FTEs
FY 1991	$6,850,000	31
FY 1992	8,168,000	38
FY 1993	9,223,000	44
FY 1994	9,967,000	45
FY 1995	11,023,000	43

Rationale for the Budget Request

The FY 1996 budget request for intramural research is $11,468,000, an increase of $445,000 over the FY 1995 level of $11,023,000. The following highlights a few research activities in the NIDCD intramural research program:

Progress in Developing an Otitis Media Vaccine

Otitis media is a major public health problem affecting young children. Although nontypable Haemophilus influenzae (NTHi) is a major pathogen, the exact cellular and molecular mechanisms involved in the pathogenesis of the bacterium-induced otitis media are not known. NIDCD intramural scientists are attempting to identify an antigen candidate for a vaccine against otitis media, using NTHi lipooligosaccharide (LOS)-derived oligosaccharide-protein conjugates. The lipooligosaccharide (LOS) is an endotoxin and a major surface antigen of this microorganism, and human antibodies against it kill the bacterium.

An effective method to purify and detoxify the LOS has now been developed. NIDCD intramural scientists are attempting to develop a detoxified endotoxin-based protein conjugate vaccine against otitis media in young children.

Molecular Basis for the Morphogenesis of the Inner Ear

Using the chick as a model, NIDCD intramural scientists are attempting to identify genes that are important in the normal development of the inner ear. The inner ear undergoes elaborate structural changes during development. Intramural scientists have found that bone morphogenetic proteins (BMP) 4, 5 and 7 are expressed during early inner ear formation known as the otocyst. The expression is different for each of the BMPs during the development of the otocyst. However, by embryonic day 2.5, the expression of all BMPs starts tc become restricted to the future ampullae, which hold the sensory structures for balance. BMPs are expressed in the sensory part of the otocysts prior to any sign of sensory differentiation. These results suggest that differentiation into sensory and nonsensory structures in the inner ear occurs early in development. Disturbance of this developmental process leads to functional deficits. Knowing the molecular mechanisms for sensory cell differentiation is critical to understanding not only sensory cell regeneration but genetic hearing and balance disorders as well. Efforts to identify genes important to inner ear development will continue.

Factors in Development of Vocal Tract Neoplasms

Tumors of the vocal tract destroy the ability of the organs of voice and speech to function and may prove life-threatening. NIDCD intramural scientists working with collaborators at the University of Michigan, Georgetown University, Johns Hopkins University and the National Cancer Institute have detected a relationship between the altered expression of molecules involved in cell adhesion and the spread of squamous cell papillomas and carcinomas in the vocal tract. Because this altered expression is an early marker of neoplastic change, it may prove to be useful in early diagnosis of vocal tract neoplasms using microscopic and molecular methods. The degree of altered expression is correlated with higher proliferation rates and more aggressive behavior of the neoplasms in patients. Further work will determine how the changes in expression may be involved in controlling tumor formation, invasion, and spread. It is hoped that the molecules involved in these mechanisms may provide a new type of target for therapy aimed at blocking tumor cell attachment and spread.

NIDCD scientists have identified four growth factors produced by tumor cells which at high concentrations may contribute to disruption of normal immune defenses and metabolism. The factors can overstimulate leukocytes which do not provide the patient with immune protection and induce general wasting of bone and body protein. These findings are helping to guide the development of gene and immunotherapy targeted at these disorders.

Gene and Immunotherapy of Neoplasms Affecting Human Communication

Investigators have performed gene therapy in an experimental model of the most common type of tumor of the vocal tract and found that two cytokines (immune hormones) can induce the immune system to inhibit growth of these tumors. Cytokines interleukin 2 and interleukin 12, which can induce killer T lymphocytes, appear to hold the most promise for immunotherapy of these tumors. A third cytokine, interferon gamma, has a direct inhibitory effect upon the growth of tumor cells. The investigators are using a nonreproducing virus to package and transfer to the tumor cells the genes that encode the cytokines needed to signal the immune system. Additional studies will determine whether immune cells from patients stimulated in this way can be useful in therapy.

Normal Physiology, Pathophysiology and Treatment of Voice Disorders

NIDCD has been studying patients with vocal cord movement disorders including a disorder called "adductor spasmodic dysphonia" in which the vocal cords close too tightly during speech and another disorder known as "abductor spasmodic dysphonia" in which the vocal cords open inappropriately during speech. Other disorders under investigation are vocal tremor and vocal cord paralysis. Investigators have found that the laryngeal reflexes in these patients differ from normal and that nerves that control the opening and closing of the vocal cords may have been damaged in these patients. Animal studies are currently underway to determine the effects of acute and chronic nerve injury on the pathways involved in laryngeal control.

The NIDCD plans to develop a novel treatment for patients with laryngeal motor control disorders affecting speech and swallowing functions. This treatment involves functional neuromuscular stimulation of selected laryngeal muscles to aid patients with intact motor neurons in controlling the valving functions of the larynx.

Waardenburg Syndrome

Waardenburg syndrome is characterized by hereditary hearing impairment, one blue eye and one brown eye and a white forelock. Mutations within the PAX3 gene have been identified as causing Waardenburg syndrome. Investigation of two families with Waardenburg Syndrome type I has identified two different point mutations in the PAX3 gene. The gene is important in the binding of DNA and in influencing transcription.

Other intramural scientists have made progress in Waardenburg syndrome, type 2 (WS2). Melanocytes are essential for the development of the eye, skin and ear. Scientists had analyzed a transgenic mouse with an insertional mutation associated with deafness and pigmentary changes. Using the junction of DNA of the inserted gene as a probe, a cDNA library of the human melanocyte was screened. A cDNA was cloned, designated as MITF (microphthalmia-associated transcription factor), and mapped to chromosome 3p14.1-p12.3. Mutations were found in MITF of WS2 families.

These investigators further analyzed the gene by transfecting it into NIH/3T3 cells and found that aberrant expression of the MITF gene can induce the differentiation of melanocyte-like cells and the production of melanogenic marker proteins. Therefore, it is most likely that the MITF gene is a gene responsible for melanocyte differentiation and for WS2, a syndrome of melanocyte depletion. Continued work will shed even more light on the genetic aspects of Waardenburg Syndrome.

National Institute on Deafness and Other Communication Disorders

Research Management and Support

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
80	$7,540,000	71	$7,836,000	70	$7,973,000	-1	+$137,000

This activity provides the staff and resources for the scientific leadership and overall management and direction of the Institute. It is composed of the staff of the Office of the Director and the Extramural Program. It involves a wide range of functions, including administration, financial management, personnel, data systems, public information activities, management of the Institute's diverse grant portfolio, and epidemiology activities.

Funding for the Research Management and Support during the last five years has been as follows:

	Amount	FTEs
FY 1991	$6,346,000	66
FY 1992	7,390,000	84
FY 1993	7,215,000	89
FY 1994	7,540,000	80
FY 1995	7,836,000	71

Rationale for the Budget Request

The FY 1996 budget request for research management and support is $7,973,000, an increase of $137,000 over the FY 1995 level of $7,836,000.

NIDCD Partnership Program

The NIDCD Partnership Program is designed to maximize opportunities for underrepresented minority individuals to participate in fundamental and clinical research on hearing, balance, smell, taste, voice, speech and language. The Partnership Program provides opportunity in a wide range of basic and clinical research including molecular biology, molecular genetics, vaccine development, development of treatment and study of its efficacy in all areas of human communication. This pilot program is a collaboration among the NIDCD, four academic centers, and the Office of Research on Minority Health at the National Institutes of Health. The participating academic centers that have minority students, faculty and staff who are underrepresented in biomedical and behavioral research are: Morehouse School of Medicine/Atlanta

University Complex, University of Puerto Rico School of Medicine/University of Puerto Rico, University of Alaska System, and Gallaudet University. Plans are to increase participation in this exciting program.

Otitis Media Among Native American Children

The NIDCD, in collaboration with the Office of Research on Minority Health at NIH and the Indian Health Service, is sponsoring a population-based study of otitis media in Native American children starting in late 1995. The study will determine the prevalence of acute and chronic otitis media and middle ear effusion in different Native American populations in the U.S. The protocol will address several known epidemiologic risk factors for otitis media. These risk factors include: infant feeding practices, passive smoking, day care enrollment, and number of other siblings in the household. The study will also investigate potential risk factors, such as prone sleeping in infancy. It is proposed that the study population include families living both on and off reservations. Communities included will come from the Northwest, Southwest, Central/Great Plains, and Southeast. Particular attention will be paid to the follow-up of and outcome in children receiving different treatments. These treatment differences will include antibiotics, sulfonamides, insertion of tympanotomy tubes and traditional remedies. The study will follow infants from birth through first grade and possibly through third grade.

227

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Full-time Equivalent Employment (FTE)

	1994 Actual	1995 Appropriation	1996 Estimate
Office of the Director...........	10	9	9
Office of Administration..........	36	33	32
Division of Intramural Research...	45	43	43
Division of Extramural Activities.	19	16	16
Division of Communication Sciences and Disorders..........	15	13	13
Total, NIDCD.................	125	114	113

Average GS/GM Grade

1990................	9.5
1991................	9.6
1992................	9.6
1993................	10.0
1994................	10.0
1995................	10.0
1996................	10.0

NOTE: Includes FTEs associated with HIV research activities. Funds to support theses FTEs are included in the NIH Office of AIDS Research.

Program Administration
Detail of End of the Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive level I	---	---	---
Executive level II	---	---	---
Executive level III	---	---	---
Executive level IV	---	---	---
Executive level V	---	---	---
Subtotal	---	---	---
Total- Exec. Lev. Sal	---	---	---
ES-6	---	---	---
ES-5	1	1	1
ES-4	4	4	4
ES-3	---	---	---
ES-2	---	---	---
ES-1	---	---	---
Subtotal	5	5	5
Total- ES Salary	$545,500	$556,410	$567,538
GS/GM-15	7	7	7
GS/GM-14	16	15	15
GS/GM-13	9	8	8
GS-12	12	11	11
GS-11	13	11	10
GS-10	2	1	1
GS-9	5	5	5
GS-8	4	4	4
GS-7	15	14	14
GS-6	10	9	9
GS-5	---	---	---
GS-4	1	1	1
GS-3	1	1	1
GS-2	---	---	---
GS-1	---	---	---
Subtotal	95	87	86
Grades Established by Act of July 1, 1944 (42 U.S.C. 207)			
Assistant Surgeon General	---	---	---
Director Grade	---	---	---

Senior Grade	---	1	1
Full Grade	---	---	---
Senior Assistant Grade	---	---	---
Assistant Grade	---	---	---
Subtotal	---	1	1
Ungraded	---	---	---
Total Permanent Positions	118	110	109
Total Positions- End-of-Year	133	125	124
Total (FTE) End of Year	125	114	113
Average ES level	4	4	4
Average ES salary	$109,100	$111,282	$113,507
Average GS/GM grade	10	10	10
Average GS/GM salary	$43,302	$44,168	$45,051

WEDNESDAY, MARCH 22, 1995.

NATIONAL INSTITUTE OF NURSING RESEARCH

WITNESSES

DR. SUZANNE S. HURD, ACTING DIRECTOR,

DR. PATRICIA GRADY, DIRECTOR DESIGNATE

DR. TERESA RADEBAUGH, DIRECTOR, DIVISION OF EXTRAMURAL PROGRAMS

WILLIAM RUSS, EXECUTIVE OFFICER/ACTING BUDGET OFFICER

DR. HAROLD E. VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. The subcommittee will come to order.

We continue our hearings today on the National Institutes of Health, beginning with the National Institute of Nursing Research. And Dr. Hurd, we're pleased to welcome you and your colleagues here today. We look forward to your testimony as Acting Director. We're pleased to learn that the new Director has just been appointed for the Institute, Dr. Patricia Grady. Congratulations. She has served very ably as the Acting Director of the Neurology Institute.

And I imagine, Dr. Hurd, that you're pleased as well, having juggled two jobs over the last months. I'm sure Dr. Lenfant is anxious to get you back to the Heart Institute on a full-time basis after your fine work at the Nursing Institute.

So we welcome all of you today. Why don't you introduce the remaining people at the table, and then proceed.

INTRODUCTION OF WITNESSES

Dr. HURD. Thank you, Mr. Chairman.

I would like to introduce the people on my left, Dr. Teresa Radebaugh, Director of the Division of Extramural Programs, National Institute of Nursing Research, and Mr. William Russ, the Executive Officer and Acting Budget Officer.

I will turn the introductions over to Dr. Varmus.

Dr. VARMUS. As usual, Mr. Porter, you are one step ahead of me here. My job is to introduce Dr. Grady, which you have done with your usual elegance. And I just remind you that Dr. Grady is a well-trained physiologist and a nurse and has served extremely ably as both the Deputy Director and the Acting Director of the National Institutes of Neurological Disorders and Stroke. We are very pleased to have her take on the leadership position of this Institute, starting in April.

OPENING STATEMENT

Dr. HURD. Mr. Porter, I appreciate the opportunity to discuss the research programs of the National Institute of Nursing Research, where I have had the privilege to serve as Acting Director for the past eight months, while as you noted, I continued my work as the Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute.

In my short time with the National Institute of Nursing Research, I have been impressed that the programs respond to many pressing health problems of the Nation. The mission of the National Institute of Nursing Research is very ambitious: to reduce the burden of illness and disability; to improve health-related quality of life; and to establish better approaches to promote health and prevent disease.

An important goal of the Institute's programs is to translate findings from basic and clinical research programs of other Institutes to impact on the health and well-being of the American public. Significant economic savings and increased productivity can result from the National Institute of Nursing Research programs designed to improve health and avoid prolonged hospitalization.

A dominant theme of the Institute is to link biological and behavioral research. Let me provide an example which is a problem familiar to everyone, whether young or old, rich or poor. I refer to acute and chronic pain. This common, highly subjective, sensory experience has alluded clear scientific definition and adequate treatment.

While basic research supported by other Institutes of the National Institutes of Health tackles such items as the neurophysiology of pain, research sponsored by the National Institute of Nursing Research investigates methods to understand, predict or reduce the intensity and frequency of this often excruciating experience.

Recent findings are clear. The consequences of pain must not be underestimated. Pain itself may alter the immune system, and hinder recuperation from disease. In fiscal year 1996, the National Institute of Nursing Research plans collaborations with other Institutes to expand research on pain that includes studies of neurochemical influences on how an individual perceives pain; the regulation of pain signals to the brain; and how the molecular mechanisms of pain interact with such variables as gender, genetic differences, cultural heritage and neurological changes. Control of pain does speed recovery with clear implications for reducing the economic burdens of illness. Research sponsored by the National Institute of Nursing Research is making valuable contributions to this important medical problem.

Another research priority for the Institute is Alzheimer's disease. Although human and financial costs of this disease are intolerably high, information on the cause, prevention and treatment of Alzheimer's disease remains almost non-existent. Yet, it is anticipated that prevalence will continue to escalate with the increased longevity of our population.

While scientists from other institutes continue to develop better approaches to therapy, research programs of the National Institute of Nursing Research focus on ways to manage symptoms such as wandering or disruptive vocalizations and to modify the social environment for patients, their families, and caregivers to preserve the patient's independence and their ability to function. The economic implication of this research is very important, because patients can remain at home longer under family care rather than entering expensive institutions.

Let me turn to a new direction for this Institute. We are an important partner in studies of the application of molecular genetics to human disease. Patients and their families need help in choosing whether and when to undergo genetic screening, given the possibility of abruptly pessimistic or unresolvable results.

The National Institute of Nursing Research currently supports research on the psychosocial and clinical impact of genetic tests in families with a history of cancer. But further research on counseling and teaching strategies is urgently needed to prepare for the revolutionary changes from molecular genetic discoveries.

The National Institute of Nursing Research will continue its important research efforts on women's health issues, such as methods to encourage wider use of breast self-examinations, particularly among older or under-served women who are at special risk for this disease. We will continue to emphasize research programs on health promotion and disease prevention for ethnic minorities, particularly in rural areas. For inner city teenage women at risk for HIV infection, and for young children, in order to halt early formation of unhealthy behaviors.

In conclusion, Mr. Chairman, balancing high quality health care and cost containment is a challenge faced by our Nation. In its short history, research sponsored by the National Institute of Nursing Research has already provided important contributions to these goals, and the future promises even greater achievements. It has been an honor and a privilege to have served as the Acting Director of this Institute for the past eight months.

I will be pleased to answer questions.

[The prepared statement and biography of Dr. Suzanne Hurd follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Acting Director
National Institute of Nursing Research

I appreciate the opportunity to discuss research programs of the National Institute of Nursing Research, where I have served as Acting Director for eight months while continuing my work as the Director, Division of Lung Diseases, National Heart, Lung and Blood Institute. In my short time with the National Institute of Nursing Research, I have been impressed that the programs respond to many pressing health problems of the nation.

The Institute's mission is ambitious: to support and conduct research and research training to reduce the burden of illness and disability; improve health-related quality of life; and establish better approaches to promote health and prevent disease. An important goal is to translate results from basic and clinical research to impact on the health and well-being of the American public. Significant economic savings and increased productivity of our citizens can be realized from research findings that improve health and avoid prolonged hospitalization or institutionalization.

A dominant theme of the Institute is to link biological and behavioral research. An example is provided by a problem familiar to everyone, young and old, rich and poor: acute and chronic pain. This common, highly subjective sensory experience has eluded clear scientific definition and adequate treatment. While basic research investigators supported by other NIH Institutes are tackling the neurophysiology of pain, research sponsored by the National Institute of Nursing Research investigates methods to understand, predict, or reduce the intensity and frequency of this often excruciating experience. While it was once thought that pain itself was something to be tolerated, recent research makes it clear that consequences of pain must not be underestimated; there is now good evidence that pain itself may alter the immune system and hinder recovery from disease.

Research is under way to develop and evaluate methods to measure pain in infants, young children and others who cannot adequately express the pain they feel. The Institute also works with cancer biologists to study pain management in patients undergoing cancer chemotherapy, as well as the interrelationship of pain from breast cancer surgery with hormonal balance and the immune system. In collaboration with other Institutes, a goal is to expand research on pain. More must be known about neurochemical influences on pain perception; regulation of the transmission of pain signals to the brain; and interactions of molecular mechanisms of pain with such variables as gender, genetic differences, cultural heritage, and neuroendocrine and neuroimmune changes. Control of pain speeds recovery, with clear implications for reducing the economic burdens of illness.

Another priority is Alzheimer's disease, which mainly affects the older population. Although human and financial costs are intolerably high, knowledge of the cause and prevention of this devastating disease remains insufficient, and treatment strategies are almost nonexistent. Yet prevalence will continue to escalate with the increased longevity of our population. In the absence of therapeutic information, our research programs focus on ways to manage symptoms and modify the social environment for patients, their families, and caregivers, so that independence and ability to function can be preserved and costly institutionalization avoided as long as possible.

Clinical research is needed to test methods to improve sleep-wake patterns for victims of Alzheimer's disease and prevent or modify wandering and aggressive and disruptive vocalizations, such as screaming, which are so disturbing in institutional settings and so shattering to caregivers in the home. Many studies include the development and evaluation of effective models for the role of the family caregiver as part of the management team. This, too, has important economic implications, because of the potential to increase the time the patient can remain in the home under family care.

Older people are also vulnerable when they are returned to the home in an unstable condition after being discharged from the hospital early. Shorter hospital stays are a general trend, and more research is needed to test hypotheses concerning treatment strategies for satisfactory recovery. A strategy being evaluated for older people hospitalized for nonsurgical cardiac treatments, for example, has shown that discharge planning and telephone follow-up at the residence by clinical experts have had positive effects on patients' recoveries, with important additional benefits of reduced demand for hospital readmissions and lower rehospitalization costs.

The rapid introduction of knowledge about molecular genetics and its application to human disease is truly remarkable, and the National Institute of Nursing Research is an important partner in this work. Methods need to be developed and evaluated to help patients and their families choose whether and when to undergo genetic screening, given the possibility of abruptly pessimistic, unresolvable results. For example, the Institute currently supports research on the psychosocial and clinical impact of genetic tests in families with heritable cancer.

Many additional questions remain, however, and development of further research on counseling and teaching strategies are urgently needed to assist individuals in making decisions. Now that some genetic defects can be detected early enough to have a chance to improve health, what choices must be made once genetic predisposition for a serious or fatal disorder is known? What are the interactions of genes with the environment and lifestyle? In sum, additional research is necessary to prepare our citizens for revolutionary changes in health care stemming from molecular genetic discoveries.

While the recent discovery of a gene related to breast cancer underscores the urgency for counseling interventions, a related issue is the importance of breast cancer screening, since early detection still continues to offer the greatest hope for successful treatment. Unfortunately, it is estimated that nearly one-third of American women fail to make appropriate use of screening tests. In cooperation with the National Cancer Institute, we hope to lower this discouraging statistic by exploring methods to encourage use of breast self exams and regular mammograms, particularly among women who are older and at higher risk of developing breast cancer, or women who are underserved and at increased risk of dying from the disease once it occurs. Management of symptoms related to surgery and chemotherapy are also under investigation.

To a greater extent than ever before, each of us must make informed choices affecting our health, choices that are often based on ambiguous or contradictory information. Yet these decisions may save or prolong our lives. A program conducted in cooperation with the Office of Research on Women's Health will address decisions related to expensive, often-performed hysterectomies as treatment for noncancerous midlife conditions, including pelvic pain, fibroids, uterine prolapse, and endometriosis. It is hypothesized that interventions to help women, their families and their care providers make diagnostic and treatment decisions will result in increased use of effective, less costly, less invasive treatments. The economic implications could be substantial, since nearly one in three women currently undergo hysterectomy for noncancerous conditions.

Health promotion and disease prevention programs encompass key controllable aspects of avoiding life-threatening illnesses such as heart disease, cancer, tuberculosis, and AIDS, which are so costly in human and economic terms. Because of the infrequent participation in prevention programs of ethnic minorities, particularly in rural areas, the Institute supports research to develop and evaluate model programs of prevention targeted at rural populations and involving the community and the family.

The National Institute of Nursing Research also supports research in AIDS prevention. In an effort to check the alarming spread of the HIV virus in teenagers and college students, investigations focus on peer counseling for inner-city teenagers, who are at particular risk of infection. In addition, research on symptom management of AIDS is under way. Progress is being made by our intramural scientists in examining methods to manage muscle weakness, fatigue, and nutrition problems.

Another intriguing research question is how to encourage adolescents to adopt healthy behaviors to prevent serious illnesses in adulthood. Studies indicate that diet and exercise, responses to stressful situations, and tendencies to take risks are behaviors formed in early childhood. Thus the Institute is focusing on the critical developmental period of young children to determine how unhealthy behaviors can be prevented.

In conclusion, balancing the two goals of high quality health care and cost containment is a challenge faced by our nation. In its short history, research sponsored by the National Institute of Nursing Research--the hypotheses, the studies, and the conclusions--have already provided important contributions to both goals. Future research initiatives hold significant promise to contribute even more to these achievements.

Mr. Chairman, the FY 1996 budget request for the National Institute of Nursing Research is $50,159,000. I will be pleased to answer questions.

SUZANNE S. HURD

CURRICULUM VITAE

BIRTH DATE

December 17, 1939, Elmira, New York

EDUCATION

Bates College, Lewiston, Maine	B.S.	1961
University of Washington, Seattle, Washington	M.S.	1963
University of Washington, Seattle, Washington	Ph.D.	1967

POSTGRADUATE TRAINING

Postdoctoral Fellow:	University of California Berkeley, California	1967-1969

ACADEMIC AND ADMINISTRATIVE POSITIONS

Acting Director, National Institute of Nursing Research, National Heart, Lung, and Blood Institute, NIH, DHHS	1994-present
Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH, DHHS	1984-present
Deputy Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH, DHHS	1979-1984
Associate Director for Program Planning and Evaluation, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH, DHEW	1976-1978
Health Scientist Administrator, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH, DHEW	1971-1976
Grants Associate, National Institutes of Health	1969-1970

HONORS AND AWARDS

NIH Merit Award	1977
NIH Director's Award	1978
Member Senior Executive Service	1980
Public Health Service Superior Service Award	1984
Departmental Management Award	1988
DHHS Distinguished Service Award	1990
Honorary Fellow, American College of Chest Physicians	1990
Presidential Citation, American Thoracic Society	1991
Meritorious Presidential Executive Rank Award	1991

NATIONAL NURSING RESEARCH AGENDA

Mr. PORTER. Dr. Hurd, let me begin by asking if the Nursing Institute is still using as its guide the long range strategic plan developed several years ago? And if so, which priority areas does the plan identify for 1996? Have you added other priority areas that were not included in the original plan?

Dr. HURD. The plan to which you refer is the National Nursing Research Agenda. It has undergone two phases. The first was implemented when the National Institute of Nursing Research was still a center at NIH and several of its goals have been met.

Phase two was initiated a few years ago, and has a five year research plan for the future. The area of research scheduled for implementation next fiscal year is related to AIDS and HIV testing. We have held a workshop, and plan to implement new projects in this area of research.

In terms of future areas that have been proposed under this plan, I have been discussing this with Dr. Grady as there might be a way of making some modification of these future areas to bring some of the programs more in line with the priorities at NIH. These will be some of the ideas that Dr. Grady will be bringing to the Institute in future years.

PROGRAM GOALS: NATIONAL INSTITUTE OF NURSING RESEARCH

Mr. PORTER. Now, I want to ask you the question that your most severe critics would ask, and I am not one of them, but I think it's good to get an answer to this question. Some of the Members of the subcommittee that are new might wonder why the Nursing Institute is part of NIH at all, since you do not support a great deal of biomedical research. Can you review for us the mission of the Nursing Institute and why you believe it has a place within NIH?

Dr. HURD. Thank you very much for asking this question, because I feel strongly after my review of the programs during the past eight months that there is an important place for the National Institute of Nursing Research at the NIH. The research sponsored by the Institute is, of course, highly related and very collaborative with research sponsored by other Institutes. However, our research programs have different emphases. You have heard testimony during the past few days from several of my colleagues at NIH to describe some of the biological and medical research on early detection, diagnosis and treatment of illnesses such as heart disease, diabetes, cancer, and AIDS. The research programs of the National Institute of Nursing Research focus on how people react to the burden of illness and disease and on health promotion and disease prevention. I have provided some examples in my opening statement, such as pain, Alzheimer's disease, human genetics, but there are many others that I could provide as well.

The main theme is that the research programs of this Institute link biological findings from medical research with behavioral application. Our research programs address the whole person. We do not look at genes, or cells, or organs. We look at people, especially people with illness and disability, and examine how they interact with the environment in which they must live and work. Research emphasis is on promotion of health, prevention of disease, and how to reduce the burden of illness and disability with which the people must live.

Why should this Institute be at NIH? Our research programs support intervention research. Scientists, supported by the Institute, collect data. They have hypotheses. They develop, and evaluate specific models, they provide data sets. The data from the research sponsored by the National Institute of Nursing Research will eventually make its way into other parts of the agency, for example, to develop of health policies or to use in the preparation of health care guidelines.

Mr. PORTER. You seem to be prepared for that question. I am only sorry—it's an excellent answer—I'm only sorry that the new Members of the subcommittee that I referred to were not here to hear your answer.

The second part of the question is, how do you distinguish the health services research supported by the Nursing Institute from that conducted by HCFA or by the Agency for Health Care Policy and Research?

Dr. HURD. This is related to my previous statement. HCFA and the Agency for Health Care Policy and Research draw upon data that are collected from many Institutes at the NIH to use in development of policies or to write health care guidelines. We believe that the data collected from the National Institute of Nursing Research that relates to the biological and behavioral information serves as a basis for use by other agencies as they conduct their investigations.

Mr. PORTER. Thank you.

Mr. Bonilla.

Mr. BONILLA. Thank you, Mr. Chairman.

Good morning, Dr. Hurd.

Dr. HURD. Good morning.

COMMUNITY-BASED INVESTIGATIONS

Mr. BONILLA. You state in your budget justification that nursing research has shown that when cultural factors unique to specific populations are included in the design of community-based health programs, participation rises, use of certain interventions or treatments increases, and risk factors are detected earlier. Could you tell me what specific research the NINR is funding that focuses on minority health care and rural health care problems?

Dr. HURD. Yes, thank you, that is a very important question to us.

As I reviewed the research portfolio from the National Institute of Nursing Research, I was impressed with the large number of investigations supported by the Institute that target health care issues of special populations, especially at the community level. We believe this is important because there are so many diverse beliefs and experiences of people from different ethnic and cultural backgrounds.We need to understand these experiences in order to develop health care intervention.

The goal of Nursing Institute research is to develop hypotheses, and develop and test methods which ultimately could be translated into larger populations. Let me give you a few examples to help answer this question. Programs are underway to develop and test home-based education programs for Hispanic families with newly discharged, very low-birthweight babies. The hypotheses of these studies are that such intervention programs may decrease the risk of morbidity and mortality. They may improve the ability of the parents to be good caregivers in the home setting. They may prevent re-hospitalizations and they may assist parents to stimulate normal neurological development of the infant.

These programs are drawing upon information developed from biological research, and developing models for practical applications which can be used in home care settings.

I could provide other examples if you wish. We have several of them.

Mr. BONILLA. I'd appreciate that. You made a good example right there on exactly how specific in some cases that your programs can be.

Dr. HURD. We know that diseases among minority and underserved individuals, as well as those in rural areas, often are diagnosed at later stages of their illness. These people tend to seek health care services later in the disease process. Our programs are working at the community level to determine how can we make people aware of the situations in which they should seek medical care.

Mr. BONILLA. Doctor, you said that was in rural areas?

Dr. HURD. Rural areas.

Mr. BONILLA. There was another area you mentioned, I didn't catch what you said.

Dr. HURD. Rural areas. We are specifically interested in minority and under-served people who live in rural areas.

Mr. BONILLA. Rural areas.

Dr. HURD. Correct. Let me give you two examples. One is a program which is looking at teaching techniques of early cancer diagnosis through breast cancer screening, or colorectal cancer screening, targeted to older African American citizens. These programs are being developed through rural community churches. If these models are successful, they can be transferred for use in other populations.

Another research area which I have found very interesting are programs specifically targeted towards Native American communities to develop and test interventions to reduce some of the specific risk factors that are faced by the Native American population, such as substance abuse, obesity and poor nutrition.

We know that these are risk factors for many diseases from studies conducted by other Institutes. Our programs are putting them all together by working with the Native American populations. The work is actually done in the community, often with the Indian tribal leaders, within their own community settings.

Mr. BONILLA. Now, Doctor, when you talk about community-based health care, does that mean community and migrant health care centers, for example?

Dr. HURD. Yes, that certainly could be part of the program. I'm not aware of any specific work that we do at the present time with migrant workers. However, we plan to implement new programs this year. I believe that my predecessor, Dr. Hinshaw, described those programs to you last year.

There was a considerable interest in the Congress for the National Institute of Nursing Research to undertake even more community-based programs this fiscal year. Thus, we have a program out for competition. One of the areas that we would be interested in supporting is research related to the migrant health population.

DISEASE PREVENTION IN RURAL POPULATIONS

Mr. BONILLA. Good, because that's a population that often gets overlooked. And so that's good to hear.

Doctor, you stated in your testimony that NINR supports research to develop model programs of prevention targeted at rural populations and involving the community and the family. Are churches involved as well in getting the word out in rural communities about prevention?

Dr. HURD. Yes.

Mr. BONILLA. One of the reasons I ask that is because in many cases, I'm not trying to get religion injected into this whole issue, but it's simply because they're the most respected organization in the community, or they can be.

Dr. HURD. Yes, again let me mention this particular program, or some of the programs that we have underway in the community. Let me again, I keep emphasizing this, but I think it is so important, that our job in the National Institute of Nursing Research is to support research to develop models and to evaluate whether they are effective. If they are effective, then they can be expanded into wider populations through other sources.

Some of our programs are extremely specific, and some of the ones in relationship to the churches are being aimed at specific populations, such as older African Americans. The specific goal is related to early detection of breast cancer. There are other programs related to child bearing women, focusing on early prenatal care. These are conducted through community churches where caregivers and parents are brought together and taught effective ways of managing the problems associated with low-birthweight infants.

Mr. BONILLA. That's good, because especially in minority areas, and I didn't point that out in my question, they have a much greater influence than in the rest of the population.

Dr. HURD. Yes.

WOMEN'S HEALTH RESEARCH

Mr. BONILLA. Doctor, tell me about the area of women's health research and what you're doing in that area.

Dr. HURD. Approximately one-third of our budget is to support women's health research. It is a very high priority for us. The major goals of our programs related to women's health are to develop and evaluate methods by which women make choices on their own health and their own medical treatment. There are several programs designed to understand normal developmental changes and the accompanying symptoms.

For women undergoing menopause, we support research to enable them to understand how to apply some of the current therapeutic approaches that are now available. For example, making decisions on the use of hormone replacement therapy for prevention of heart disease that you heard described by Dr. Lenfant during his testimony in the Heart, Lung, and Blood Institute.

We have several programs on breast cancer screening. Many of these are supported in collaboration with the National Cancer Institute. Our programs are specifically geared towards some of the older Americans in the rural communities. We can try to reach some of these special populations through programs designed to explore how these populations can use techniques of breast cancer screening to prevent the development of disease.

A recent program, undertaken this year, relates to decision making in seeking treatment for invasive procedures, such as hysterectomy. I have to admit, I was very surprised when I came to the National Institute of Nursing Research to learn that hysterectomy is the second most commonly performed major surgery for women in the United States. Half of the hysterectomies are performed on women who are 40 years old or younger, noting there is considerable regional variation in this procedure. We have a program that we are developing this year to try to determine how women can make decisions that will prevent unnecessary surgeries from taking place when there are other options for consideration.

Perhaps next year when Dr. Grady is testifying in front of this committee, she will be able to provide some results of this interesting research.

Mr. BONILLA. We always look forward to hearing from Dr. Grady.

Mr. Chairman, since it's just us this morning, may I continue with a couple more questions?

Mr. PORTER. Surely.

ALZHEIMER'S DISEASE

Mr. BONILLA. I walked in about the time you were mentioning Alzheimer's in your opening remarks. Could you just elaborate a little bit more on the research that you're doing in that area?

Dr. HURD. Let me emphasize that the research programs of the National Institute of Nursing Research on Alzheimer's disease are done in very close collaboration with colleagues at other Institutes, the National Institute on Aging and the National Institute of Neurological Disorders and Stroke.

However, our research programs are designed specifically to look at the behavioral aspects of Alzheimer's disease, how can we work with patients, their families and their caregivers to try to understand some of the behavioral symptoms that are involved in this devastating disease.

Some of the specific research programs that are underway at our Institute are trying to understand what kinds of factors lead to specific behavioral problems. What is the relationship between these behaviors and the advancing neurological damage that these people face? What neurological and motor changes occur that contribute to important health problems, such as urinary incontinence? The Nursing Institute has a long history of research to develop methodology to prevent urinary incontinence in older Americans. The question is, will some of these programs have an effect on people with Alzheimer's disease, and if so, can we keep these people out of institutions as long as possible.

In summary, our programs are very related to the behavioral problems of Alzheimer's.

NURSING SCHOOLS

Mr. BONILLA. I have a question now that's related to something Chairman Porter asked earlier. We're especially proud, of course, in South Texas of the School of Nursing in the UT Health Science Center. You probably know that we just had a huge expansion of the School of Nursing and we're very proud of that. Enrollment for nursing has increased by 774 students there, and more than 300 qualified students could not be admitted.

I understand enrollment is up nationwide in masters degrees in nursing and RNs returning to school for bachelor of science degrees. I just want to quote Dr. John Howe of the UT Health Science Center, who's president there. He says, "From RNs to Ph.D.s, nurses are one of the vital centers of our health care delivery system." My question is, how does NINR interact with the more than 500 nursing schools like the one at the UT Health Science Center?

Dr. HURD. We would like to believe that we are good partners with all of the nursing schools throughout the Nation, and we have very close relationship with many of the major nursing organizations. In fact, some of them are here listening to this testimony. We have had very good relationships with many of the institutions. We participate in many of the meetings to discuss issues that you describe, such as developing nursing schools. Most important to the National Institute of Nursing Research is the question of when in the career of a nurse they should enter into research, that is, when to have research as part of their training.

One of the important parts of our budget is research training for the National Institute of Nursing Research. You might notice in looking at some of the figures that our Institute has put considerable support into training in the past several years; I would think that Dr. Grady will want to continue this effort in the future.

There was a recent report from the National Research Council that recommended increased support for training for nurse scientists. They recommended a level that doubles our current level, from 208 to 500 each year. That is a big jump and it will be impossible for us to meet that.

We are working together with some of the voluntary organizations to try to determine how to increase the numbers of nurse scientists, how to work with the voluntary organizations, and how to encourage additional training opportunities through the intramural programs at the NIH so that we can continue to do the research that's required by the National Institute of Nursing Research and continue to train the people that need to be trained.

Mr. BONILLA. Dr. Hurd, thank you. I'd appreciate if just for the record you'd provide me with some more information about research on pain as well. So if you'd just do that for the record, I'd appreciate it.

Dr. HURD. Okay.

[The information follows:]

RESEARCH ON PAIN

The management, control and alleviation of pain is a critical national health problem resulting in nearly 40 million physician visits each year with costs, direct and indirect, or over $100 billion per year. The National Institute of Nursing Research (NINR) has been a leader in research on pain. The assessment of pain in infants and children has been especially problematic since these patients are often unable to accurately communicate information about their pain. NINR has already made substantial contributions in this area of research. NINR-supported studies have addressed pain in infants, including identification of specific behaviors, vocalization, physiologic measures, and other cues that help to identify the level of pain in this special population. Other investigations have evaluated the analgesic effect of medication in children and adolescents who have undergone surgery. Methods appropriate to the age of the child have been developed to identify location, quality, intensity, and other pain dimensions. This latter study resulted in a word graphic rating scale that has been incorporated by the Agency for Health Care Policy and Research in practice guidelines for the management of acute pain. In response to a recent initiative regarding factors associated with assessment, management, and prevention of acute pain, a number of critical new studies are being undertaken by NINR grantees. These studies address a range of issues, including improving pain management with combinations of opioid and non-opioid drugs; enhancing the effectiveness of patient-controlled analgesia; and determining the potential of post-operative pain management to offset the increase in metastasis resulting from surgery. Improved understanding of the pain experience and its treatment in special populations, such as cognitively impaired children and older adults in long-term care settings, is also among these new investigations. Researchers are also examining interventions for post-operative pain and their cultural relevance for children of African-American, Hispanic, and European-American backgrounds.

Mr. BONILLA. I noticed your system of flipping cards. That works very well. I should do that as well. Every 15 minutes of the day sometimes we're expected to be experts on health care, on defense systems, on foreign aid, so it seems like it works very well for you.

Dr. HURD. I've been telling my colleagues this is really like my final exam, so I have a lot of crib sheets here.

Mr. BONILLA. Thank you, Dr. Hurd.

Dr. HURD. Thank you.

STAFFING LEVELS AT NINR

Mr. PORTER. Dr. Hurd, while all Institutes must be expected to bear their share of the personnel downsizing burden at NIH, the small Institutes, such as yours, may have less flexibility to absorb staff cuts. What FTE targets does your Institute have, and has NIH leadership made any accommodation to your situation so that you can maintain a critical mass of staff?

Dr. HURD. Yes, indeed, the National Institute of Nursing Research is a small Institute. However, we feel strongly that to meet the commitments of the nurse scientist community, the Institute must be run effectively and efficiently. In this regard, like all other Institutes at NIH, we have been examining our current staffing levels.

We have been working within the Institute to develop management teams and job sharing so that there are some flexibilities of work load balances. We have been helped by the leadership at NIH in the reduction of the numbers of reports, the amount of paperwork, and especially the streamlining of the grant applications process.

We feel strongly that we can continue to support all of the functions of the Institute if we tighten our belts a bit. But we also feel very strongly that we do have a responsibility to the work of the nurse scientist. We believe we can do this effectively with the resources that we are provided.

SUCCESS RATES

Mr. PORTER. Your Institute has the dubious distinction of having the lowest projected success rate on campus in 1996 of about 12 percent. We've discussed this problem in previous years. What trends are you seeing in your applicant pool and how do they affect the success rate?

Dr. HURD. That is a very interesting question, and I am glad you asked it. It is one that has taken my attention in the last eight months, because the first day I arrived on the job, I had a letter which required a response. And so I have looked at this situation very closely.

Indeed, it would appear overall that the success rate of the National Institute of Nursing Research is significantly lower than other Institutes. However, if you separate the applications that are submitted by the nurse scientists themselves, which we call investigator-initiated applications, the success rate is similar to the success rates throughout NIH.

The difference comes in the large number of applications that are submitted in response to Institute solicitations. There are a large number of applications that come in response to these solicitations, which modifies the success rate. I recently wrote an editorial that appeared in one of the nursing journals that encouraged the nursing community to increase their numbers of investigator-initiated applications in a wide variety of areas. I believe the success rate is an issue that needs close attention, but it is not the same magnitude of problem that has been presented in the past.

TUBERCULOSIS

Mr. PORTER. Dr. Hurd, your Institute has been working on treatment of non-compliance for tuberculosis for several years. Do you have any findings to report for public health authorities who are trying to deal with difficult populations in prisons, homeless shelters, and long-term care facilities?

Dr. HURD. Mr. Chairman, if it would be possible, I would like to submit the response to this question for the record. We do have several projects in this area, but they were initiated just this past year. If it would be acceptable, I could present for the record information about these grants and what we would hope they would be able to achieve.

Mr. PORTER. Fine.

[The information follows:]

TURBERCULOSIS

Failure to complete recommended treatment or adhere to recommended health behaviors accounts for a significant part of the health care burden. For example, failure to complete recommended treatment by infected but symptom-free individuals has contributed to a rapid rise in the number of tuberculosis cases over the past four years. Partially or untreated patients continue to infect others in community facilities, long-term care institutions and prisons. In addition, lack of adherence to treatment regimens has resulted in an increased number of cases for which current drug therapies are not effective. Unfortunately, people who acquire tuberculosis are often the most difficult to treat as many of these individuals are homeless, alcoholics or drug abusers, and live on the margin of society. Nurses, who play a critical role in increasing the frequency with which infected individuals successfully complete therapy, need more scientifically-based information about strategies to promote adherence among difficult populations. For this reason, the Institute initiated studies of tuberculosis in 1994. Populations are being successfully recruited including Hispanic migrant workers in Arizona, inner-city Hispanic immigrants in Los Angeles, and inner city African Americans in Detroit. Areas of research emanating from the NIR initiative on tuberculosis-related studies include the development of innovative educational strategies to reach populations with high disease prevalence; testing strategies that enable health professionals to target efforts to address barriers to adherence; and testing interventions that promote adherence to prevention and treatment regimens.

Mr. PORTER. Your Institute is supporting research into AIDS prevention using such techniques as peer counseling. Is this the best use of your scarce resources when the Centers for Disease Control and Prevention supports extensive AIDS prevention efforts?

Dr. HURD. Good question. I am not quite sure that I would agree with the beginning part of the sentence. Our AIDS research programs are related to a much broader aspect of research than techniques of peer counseling. We have a large, actually a considerable, portfolio in research related to AIDS.

But most of the research on AIDS is related to symptom management, specifically related to the problems people face due to nutritional changes; research related to fatigue; research related to muscle weakness from drug therapies. A wide variety of symptoms, again, putting together pieces that are developed through many other Institute programs. The NINR puts them together, looking at the whole patient and how they are responding to their therapy. Peer counseling and caregiver input is one piece of the effort. But it is a very minor piece compared to looking at a variety of physiological, biological and behavioral responses.

Mr. PORTER. Thank you.

Mr. Stokes.

ALZHEIMER'S DISEASE

Mr. STOKES. Thank you, Mr. Chairman.

Good morning, Dr. Hurd.

Dr. HURD. Good morning, how are you?

Mr. STOKES. I am fine, how are you? It is good to have you here.

You may have covered this area while I was tied up with another subcommittee. However, it is an area that I'd like to talk with you about. Dementia associated with Alzheimer's disease and stroke is a major health problem. It takes a tremendous toll on the individuals suffering from these diseases, along with their families. With respect to progress stemming from nursing research, what can you tell us this year that you could not tell us last year about it?

Dr. HURD. The Alzheimer's disease research programs of the National Institute of Nursing Research are conducted in close collaboration with other Institutes at NIH; the National Institute on Aging, as well as the National Institute on Neurological Disorders and Stroke. However, the programs of the National Institute of Nursing Research focus on the cognitive and behavioral symptoms of Alzheimer's patients.

We are very interested in research related to the memory lapses. We are also interested in research related to some of the symptoms people face such as wandering, aggressive behaviors, disruptive sleep behaviors, pacing, agitation, difficulty in dressing, and the problems of urinary incontinence. As these symptoms become difficult to manage, they result in decisions to institutionalize patients, resulting in the high cost of caring for these individuals.

The research programs at the National Institute of Nursing Research examine a variety of behavioral and mental problems in trying to look at the entire environment in which these people must work and live. Many of our programs are related to the role of caregivers, the role of the patients, and how one begins to understand some of these behavioral problems that the individuals with Alzheimer's disease face.

Many of our programs have just been initiated in the past year or so, based on a specific initiative that we undertook with the National Institute on Aging. So today I cannot provide specific results. However, my colleague Dr. Grady, who will be assuming the leadership of this Institute within the next few weeks, will be meeting with you here next year. I think that there will be many more results from this specific research that she can present to you.

If you would like, Mr. Stokes, for the record I would be more than happy to present some of the specific research hypotheses that are being tested in these applications.

Mr. STOKES. Dr. Hurd, I would appreciate it if you would expand on this question in the record for us.

Dr. HURD. Thank you.

[The information follows:]

ALZHEIMER'S DISEASE

The behavioral problems which occur during the course of Alzheimer's disease are especially difficult for patients, families and care providers. The National Institute of Nursing Research has been a leader in the support of research to understand, prevent and manage these troublesome and costly symptoms. Examples of questions under investigation include how to prevent wandering, how to recalibrate sleep-wake patterns, and how to re-establish self-dressing behavior. Investigators are also examining the effect of systematic "memory exercise" on cognitive abilities and how to improve ordinary daily communication in impaired people.

AIDS

Mr. STOKES. Let me move to another subject. AIDS has now become the leading cause of death for people ages 25 to 44 years of age. And according to the Department, every three minutes one American dies of AIDS. Tell us, what is the most significant research that's underway at your Institute with respect to AIDS?

Dr. HURD. Let me focus on the research that is conducted in the Institute's Division of Intramural Research. Although our intramural research program is small, it, too, is extremely collaborative. Our scientists work closely with scientists in the National Institute of Allergy and Infectious Diseases and in doing so, are examining individuals with HIV disease who are at NIH for treatment.

Our specific research programs focus on interventions to alleviate symptoms. We are conducting research on the interrelationship of immune function and nutritional status. We examine the impact of the drug therapy on muscle weakness. And, we study the nature and the impact of fatigue especially during treatment.

A number of these studies are underway within the National Institute of Nursing Research, but we also support extramural projects on AIDS.

MINORITY HEALTH PROGRAMS

Mr. STOKES. Dr. Hurd, for a number of years, I have been struggling on this subcommittee with a problem that relates to African Americans and other minorities, and that is the disparity in health care that exists in that population as compared to the majority population. That is something that each Institute Director has testified about before our subcommittee over the years.

Can you tell us to what extent your Institute is involved in initiatives relative to minorities, particularly in nursing research?

Dr. HURD. Mr. Stokes, among the notable strengths of the National Institute of Nursing Research programs, are studies at the community level that target the health care issues of special populations, such as minorities or people particularly vulnerable to disease.

The goal of the Institute is to examine ways to include diverse beliefs and experiences of people of different ethnic and cultural backgrounds in development of health care interventions. Many programs underway are specifically related to the African American population. For example, there are programs to develop and evaluate models to work with older African American citizens in community based programs conducted in local churches. Some of these programs look at ways of determining early cancer detection, such as breast cancer screening, as well as colorectal cancer screening in older African American communities.

We are extremely interested in research relating to women in their child bearing years to prevent the delivery of low-birthweight infants. Many of our programs are working with African American populations and emphasize the importance of good nutrition and the importance of taking care of themselves prior to the delivery of their babies.

We have a number of programs underway that work with Native American populations. We are very interested in community programs that address specific health problems that are faced by Native Americans. We are particularly interested in programs to test intervention strategies against diseases that exist in these communities, such as substance abuse, obesity, and poor nutrition. In these community-based programs, models are developed and evaluated in very close relationship with community leaders.

We have a number of programs that are based on the hypothesis that some of the work can be done at home. We have some very specific home-based education programs. Working with minority families, such as Hispanic families and African American families with newly discharged very low-birthweight babies, investigators are testing the hypothesis that intervention programs should be able to decrease the risk of morbidity and mortality of these babies once they are in their home setting. This should decrease the numbers of times that these babies must return to the hospital. We hope to figure out ways to improve how parents can be successful caregivers in these home settings. How can we assist parents to understand how to help their babies with normal neurological development.

These programs complement other behavioral and biological research that has come from other Institutes such as the National Institute of Child Health and Human Development. Our role is to develop the models that will prove to be successful in helping to reduce the burden of illness.

ASTHMA

Mr. STOKES. I'm pleased to hear that. Let me ask you about a specific area that I'm concerned about, and that is asthma. Asthma continues to be a major medical problem affecting some 10 million Americans, more than one-third of whom are under 18 years of age. We understand recent studies reveal that African Americans and Hispanics living in inner city areas may have unusually high rates of asthma morbidity and mortality. To what extent is this area of research considered a priority for your Institute?

Dr. HURD. Mr. Stokes, you could not have asked me a better question. As you might know, I currently have two roles, and my other role is, Director of the Division of Lung Diseases, in the Heart, Lung and Blood Institute, where we have a major commitment to research related to asthma, specifically in African–American populations.

Thus, I am extremely aware of the programs to which you refer. The National Institute of Nursing Research at the present time is not involved in programs specifically related to asthma. However, they are a major partner in the National Asthma Education and Prevention Program coordinated by the NHLBI. Many of the nursing organizations participate in the coordinating committee, along with the other organizations that are part of the National Asthma Education and Prevention Program.

Just recently, the National Asthma Education and Prevention Program released a document on the management of asthma for the nursing community. I expect that this will lead to a variety of new research proposals that are likely to come to the National Institute of Nursing Research. Given the history of the Nursing Institute, I believe these programs will focus on community programs, specifically in minority populations.

So I would look to that as being one of the future important goals that the Nursing Institute may very well wish to undertake.

Mr. STOKES. Thank you very much, Dr. Hurd. And Dr. Grady, I look forward to hearing from you later.

Dr. GRADY. I will look forward to reporting to you, also.

Mr. STOKES. Thank you very much.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Hurd, I don't think we asked you any question that you weren't prepared on. So congratulations to you and to your very fine staff. You did an excellent job and we will get you back to wearing just one hat and appreciate your wonderful service at the Nursing Institute. Dr. Grady, we look forward to seeing you here next year.

Dr. VARMUS. Mr. Porter, if I could, I would just like to interject one note of appreciation to Dr. Hurd. She has come from a large traditional Institute to have a look and give guidance to a small, very new Institute. And in doing so, she has provided special guidance to me, I think to the Institute and to your committee, and has set the stage for progress under its new leadership, which will begin very soon under Dr. Grady.

Mr. PORTER. Thank you, Dr. Varmus. I certainly agree with what you said.

Thank you, Dr. Hurd.

[The following questions were submitted to be answered for the record:]

PAIN

Mr. Stokes: According to the Congressional Justification, pain has a direct adverse impact on the body's ability to heal from disease. It further states that research at the cellular and molecular level is key to understanding the neural mechanisms that cause pain. Specifically, what is the Institute doing to address this problem, and to what extent is there collaboration with the Cancer Institute to address the pain associated with chemotherapy, and with the Dental Institute with respect to its pain research initiative?

Dr. Hurd: The National Institute of Nursing Research (NINR) supports both basic and clinical research on pain in close collaboration with many Institutes, including the National Cancer Institute (NCI) and the National Institute of Dental Research (NIDR). Animal studies are under way to test for gender and age differences in the neurochemical effect of analgesia during surgery for mammary cancer in rats. Previous research has shown that giving morphine during surgery decreases metastasis, but it is not known whether there are differences based on gender or age. Clinical studies include investigations of the treatment of oral pain resulting from intensive cancer chemotherapy and radiation to examine not only the biologic and clinical markers of acute oral pain, but also the accompanying emotional, cognitive, and behavioral aspects of the pain in order to intervene effectively. The NINR plans to continue its close collaboration with other Institutes to assure a coordinated approach to the study of pain while continuing its commitment to research on biobehavioral interventions to manage and prevent pain.

ALZHEIMER'S DISEASE

Mr. Stokes: Dementia associated with Alzheimer's disease and stroke is a major health problem and takes a tremendous toll on the individuals suffering from these diseases and their families. With respect to progress stemming from nursing research, what can you tell us this year that you could not tell us last year?

Dr. Hurd: Since there are no definitive treatments yet for individuals with dementia associated with Alzheimer's disease and other disorders, we believe it is critical to examine symptoms which are most troublesome for patients, families and caregivers. These symptoms, such as wandering, urinary incontinence, screaming, and sleep problems, usually lead to costly institutionalization. The NINR, in collaboration with the National Institute on Aging (NIA), has initiated research designed to examine these important physiological and behavioral issues. Preliminary findings are providing promising directions for further research. For example, there are indications that "white noise" may have a calming effect on nursing home residents who exhibit disruptive vocalizations. Screaming behaviors appear to be less frequent in the morning, but gradually increase to a peak in the late evening. The disruptive behaviors also appear to decrease in the presence of other people or during mealtimes. These and other findings need to be tested in larger-scale clinical studies to improve the care of patients and decrease the burden of family caregivers.

Mr. Stokes: What portion of the Institute's budget is invested in this research area, and how does it compare with the FY 1995 and 1994 funding level?

Dr. Hurd: The FY 1996 budget request includes an estimated $3,370,000 for research on Alzheimer's disease, which equates to approximately 6.7 percent of the Institute's total 1996 budget request. The FY 1996 spending level demonstrates the Institute's increasing commitment in this area, and compares favorably to the $3,122,000, or 6.1 percent of the total appropriation that was spent on Alzheimer's disease research in FY 1994. In FY 1995, NINR expects to spend $3,230,000 on Alzheimer's disease, which is 6.7 percent of the FY 1995 appropriation.

MINORITIES IN RESEARCH

Mr. Stokes: To what extent are there initiatives underway at your institute that ensure and expand the participation of African Americans and other minorities in nursing research?

Dr. Hurd: Among the notable strengths of the research portfolio of the NINR are studies at the community level that target health care issues of special populations, such as minorities, or others particularly vulnerable to disease. The diverse beliefs and experiences of people of different ethnic and cultural backgrounds are integral to the Institute's development of health care interventions. In addition, the Institute has a long-standing commitment to increase the diversity of scientists in research. Institute staff frequently meet with college and university faculty to discuss opportunities to increase participation of minority scientists in the Institute's research portfolio. The strongest indicator of the Institute's commitment has been the provision of supplements to research grants for underrepresented minorities. For FY 1994, the Institute ranked second among all the Institutes at the NIH in the proportion of research grant funds to support supplements for minority students or investigators.

ELDERLY AND THE OLDEST OLD

Mr. Stokes: The elderly are one of the fastest growing segments of the population. In fact, by the year 2030, the U.S. population age 65 and older is expected to double. What research is underway to address the challenges in treating and caring for the elderly and the oldest old?

Dr. Hurd: The future of research sponsored by the NINR is promising with respect to its potential to sustain and improve the quality of life for older Americans. Further, the Institute is poised to provide data relevant to cost-effective programs for older adults and for the anticipated wave of individuals now in their third and fourth decade of life who are expected to exert unprecedented demands on health care resources during the first decades of the 21st century. A major focus of the Institute's behavioral research efforts is targeted to the challenges in treating and caring for older adults and the oldest old by caregivers, usually women, who are responsible for elderly relatives. Frequently, caregiving results in excess burden and frustration leading to termination of the care and resulting in costly institutionalization. The Institute also supports research on effectiveness of comprehensive discharge planning for older adults who are often discharged from acute care hospital beds but require more assistance after discharge. Another challenge for NINR investigators is the increased occurrence of falls in older adults and the need for sensitive balance assessment tests to determine older citizens at risk. Results from this research offer the potential for developing a practical test of balance ability that can predict the risk of falls in older adults in a variety of settings.

RESEARCH OPPORTUNITIES

Mr. Stokes: Please describe the most promising opportunities you anticipate in nursing research for the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Hurd: The NINR is poised to address a number of critical public health and patient care questions which have the potential to impact on morbidity, mortality, quality of life and cost of care. A dominant theme of the research portfolio is the linkage of biological and behavioral research. Some examples of promising opportunities relevant to the major emphasis areas of the NIH are: human genetics, neurobiology and research on health problems of older Americans.

In parallel with advances in molecular genetics, research on the sequelae of genetic predisposition to disease, associated decision-making processes, and the social and ethical issues generated by this research is crucial. Some of the important research questions include: What are the links among environmental factors, lifestyle choices, information use, and psychological adaptation in individuals and families with genetic predisposition to specific diseases? What are the physiological, psychological, and economic outcomes of gene therapy on individuals and their families? How do individuals, families, and clinicians arrive at decisions regarding the implementation of genetic testing and genetic therapy? What are the implications of cultural differences in each of these areas?

While research scientists have made remarkable progress in the neurobiology of pain, our understanding of the subjective pain experience and its management remains limited. Research supported by the NINR will focus on the effects of multiple factors such as genetic differences, endocrine and immune function, stress, age, gender, ethnicity, and cultural background on the pain experience; effective pharmacological and/or non-pharmacological interventions to prevent pain and the subsequent establishment of pain pathways; and effective pharmacological, non-pharmacological, and behavioral approaches to the management and alleviation of pain. Pain research is one area of the research related to symptom management supported by NINR.

Costs of care for patients with Alzheimer's disease are estimated at $90 billion annually. While we are not yet able to alter the clinical course of this disease, there are substantial opportunities to ameliorate symptoms and reduce the burden of care through behavioral interventions. For example, clinical studies and clinical trials are required to examine interventions to prevent and interrupt specific behavioral disturbances and to prevent and manage physical and functional problems such as falls, incontinence, and sleep disturbances. Short- and long-term consequences of the caregiving role for family members and outcomes that lead to institutional care of the patient must also be investigated. Development of interventions that delay transfer of Alzheimer's patients to more expensive, care-intensive settings are essential. The NINR, in close collaboration with the NIA, can provide important new directions through support of research in this important disease that affects so many older Americans.

Mr. Stokes: To what extent will the FY 1996 budget allow the institute to begin to implement the opportunities that are ready to be exploited?

Dr. Hurd: The FY 1996 budget request will enable us to continue our ongoing efforts as well as provide support for some new research. While there are many programs that need to be initiated to meet the Institute's mission of reducing the burden of illness and disability, there are some promising new research areas such as genetics of human disease, and other areas of expansion such as neurobiology and pain, the behavioral symptoms in Alzheimer's disease and prevention and care related to HIV disease. We anticipate that support of research in these areas will lead to the development of new clinical care procedures, new ways to prevent disease, new diagnostic tools, and better ways to provide care for the elderly.

HOME CARE

Ms. Lowey: You state in your testimony that more information is needed to test the effect of shorter hospitals stays on patient's recovery. Given that the trend, as you say, is for shorter hospital stays -- What research actually is being done on its effect, and where do you see a need for additional research? It seems to me this is research that we would all benefit from.

Dr. Hurd: There is no doubt that in-hospital medical and surgical treatments continue to have substantial impact after discharge as patients are sent home as soon as possible after the actual treatment event. However, the effects of the most perfectly designed treatments can be lost if patients do not recognize early signs of complications, do not know how to care for themselves, or fail to take necessary precautions or medications. Scientists supported by the National Institute of Nursing Research (NINR) have been developing and evaluating strategies to facilitate early hospital discharge safely so that quality of care is not jeopardized. The hypothesis is that planning for early discharge and home follow-up by a clinical nurse expert will result in fewer longer-term complications, fewer re-hospitalizations and emergency room visits, shorter lengths of stay if re-hospitalization occurs, and reduced costs of care. All of the population groups examined, including elderly people hospitalized for non-surgical cardiac problems, patients hospitalized for various elective surgeries, unplanned cesarean births, or complications of pregnancy have demonstrated positive results leading to significant reductions in costs as well as improved health outcomes. More extensive use of health programs carried out in the home and community with involvement of community members need testing to determine their effect in keeping people well and in preventing illness and disability.

Ms. Lowey: In the budget justifications you mention that home-care by nurse specialists has been found to be cost-effective. Could you discuss these findings in greater detail?

Dr. Hurd: The NINR is supporting research on the effectiveness of discharge planning and telephone home follow-up protocols to improve patient outcomes and reduce the cost of care. In this time of shortened hospital stays, patients and their families must be able to recognize early signs of complications, care for themselves, and take necessary precautions and medications. Through randomized clinical trial design, nurse specialists plan for post-discharge and provide telephone follow-ups. Several patient groups have been tested to date, including elderly patients undergoing medical treatments for cardiac disease. At 6 weeks after initial hospital discharge, only 10 percent of the group receiving the intervention after their medical treatment were readmitted to the hospital, compared to 23 percent of those receiving traditional care. Expenses for services for the medical treatment group were 63 percent less than those for the control group. In separate studies of discharge planning and home follow up models targeted to women hospitalized for elective surgery, unplanned cesarean sections, and complications of pregnancy, such as high blood pressure, cost reductions also occurred with savings varying from 6 to 40 percent. These studies need to be replicated in other populations, especially those with limited ability to care for themselves, and with other clinical problems and treatments. However, the promising results from these very specific research models support the potential expansion of these programs that are cost-effective and demonstrate quality of care.

ESTABLISHING HEALTHY BEHAVIORS IN YOUNGER CHILDREN

Ms. Lowey: The budget justifications mention that NINR supports extramural research in "establishing healthy behaviors in younger children." It seems to me that this type of work is crucial to taking a preventive approach to health care. Will you discuss this research in greater detail?

Dr. Hurd: It is true that a substantial portion of the chronic illnesses and conditions experienced in mid- and later life, such as coronary heart disease, hypertension, noninsulin-dependent diabetes mellitus, osteoporosis, and obesity are the result of choices made and behaviors adopted very early in life. It is now widely accepted that an unbalanced diet, alcohol misuse, tobacco use, lack of exercise, poor management of stress and willingness to take risks are clearly linked to chronic diseases. From intervention studies, many supported by the NINR, it is known that by the time of adolescence, behaviors have been adopted which are difficult to change. Thus, the point of intervention, education and teaching must be in early childhood.

Ms. Lowey: What are we learning about our ability to change behavior, particularly at a young age?

Dr. Hurd: The knowledge base of how young children understand health information and make choices about their own behavior is limited at best. Investigations are under way on the role of families, school and health care providers in the development of health related behaviors in older children and adolescents. For example, investigators are testing interventions in various settings to promote the early establishment of good exercise and nutrition habits, looking at the relative benefit of classroom versus small group interaction, the usefulness of summer camp or after-school programs, and the advantages of inner-city community centers or church recreation halls. This research demonstrates that these multi-dimensional approaches are necessary to obtain and maintain healthy behaviors. However, there is a need to develop programs that evaluate these methods in reaching children of elementary school age and younger.

BREAST CANCER

Ms. Lowey: I understand that you are working with the National Cancer Institute to explore methods to encourage the use of breast self exams and regular mammograms -- since nearly one-third of American women don't use these tests adequately. Could you discuss the NINR's role in this area? As you know, I have strongly supported the CDC's efforts in this area -- the breast and cervical cancer screening program -- because I feel we must educate women and their families about the importance of early detection of breast cancer.

Dr. Hurd: The National Cancer Institute (NCI), the NINR and the Centers for Disease Control (CDC) have different, yet complementary roles in the effort to educate women and their families about the importance of early detection of breast cancer. The NCI has the primary responsibility to develop scientific data regarding causes, methods of early detection and treatment of breast cancer. The NINR supports research to develop strategies to help women personalize their risk status, eliminate unnecessary fear as a barrier to action, and incorporate routine detection practices into their health habits. Nurse scientists in diverse practice settings have a wide variety of opportunities to teach and counsel women and their families. Data obtained from programs supported through the NIH institutes such as the NINR, provide the foundation for the programs of the CDC, which must assure transfer of appropriate health information to the U.S. population.

HYSTERECTOMY

Ms. Lowey: You mention that you are working with the Office of Research on Women's Health to address the issue of whether women should undergo hysterectomies for noncancerous conditions. Could you discuss this work in greater detail?

Dr. Hurd: The NINR is collaborating with the Office of Research of Women's Health (OWHR) to explore the reasons for the high rate of hysterectomies for noncancerous conditions such as fibroids, chronic abdominal pain, and frequent bleeding, that may be amenable to less invasive, less costly treatments. It is expected that women who have access to accurate information about treatment options and potential outcomes following hysterectomy will choose this surgical option less frequently.

Ms. Lowey: How does NINR fit into this research?

Dr. Hurd: NINR has long supported research in many areas of women's health. The emphasis of the research has been on normal, developmental mid-life changes; symptoms occurring in mid-life women and strategies to manage them; and mechanisms to assist women in making treatment decisions. In FY 1996, NINR will continue its women's health research program to address conditions and symptoms that result in high costs and morbidity for the American public.

GENETIC SCREENING

Ms. Lowey: You mention genetic screening, and the importance of developing counseling strategies to help individuals and families decide whether to undergo screening -- or how to deal with the possible results of screenings. I know the Genome Center is very involved in this issue. Could you discuss in greater detail the role the Nursing Institute is playing in this area?

Dr. Hurd: The NINR is an important partner in studies of the application of molecular genetics to human disease. The recent advances in molecular genetics and their implications for health care are almost incomprehensible to all but the scientific world. The resulting revolution in understanding, diagnosing, and treating many diseases will be matched by corresponding dilemmas in the choices and decisions facing patients and their families. Historically, nurses have had a major role in counseling, educating, and supporting patients and families in making treatment and health care choices. Research is urgently needed to determine how to assist patients in making decisions about testing for genetic predispositions for themselves and their children; to determine the counseling and teaching strategies that are most effective; and to examine cultural differences that must be taken into account in developing counseling strategies. It is also important to determine how risk reduction interventions can be implemented for those with genetic predisposition for specific diseases. In collaboration with the National Center for Human Genome Research (NCHGR), the NINR is supporting research on the psychosocial and clinical impact of genetic tests in families with a history of cancer. However, further research on counseling and teaching strategies is urgently needed to prepare for revolutionary changes resulting from molecular genetic discoveries.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

FY 1996 Budget — Page No.

Organization chart.......... 102

Appropriation language.......... 103

Amounts available for obligation.......... 105

Budget mechanism table.......... 106

Summary of changes.......... 108

Budget authority by object.......... 110

Administrative costs.......... 112

Significant items in Senate Appropriations Committee Reports.......... 113

Authorizing legislation.......... 114

Appropriation history.......... 115

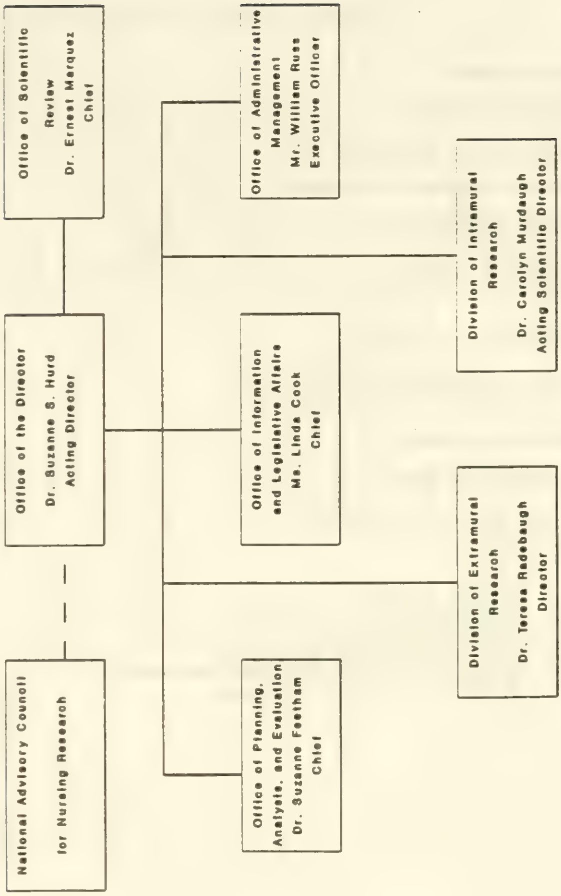
Budget authority by activity.......... 117

Justification:

A. General statement.......... 119
B. Extramural research.......... 124
C. Intramural research.......... 128
D. Research management and support.......... 130
E. Detail of full-time equivalent employment (FTE).......... 131
F. Detail of end-of-year employment.......... 132

NATIONAL INSTITUTES OF HEALTH
National Institute of Nursing Research

Organizational Structure


Office of Scientific Review
Dr. Ernest Marquez
Chief
National Advisory Council for Nursing Research
Office of the Director
Dr. Suzanne S. Hurd
Acting Director
Office of Administrative Management
Mr. William Russ
Executive Officer
Office of Information and Legislative Affairs
Ms. Linda Cook
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Dr. Suzanne Feetham
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Division of Intramural Research
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Division of Extramural Research
Dr. Teresa Radebaugh
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to nursing research, [$48,237,000] $50,159,000.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, PL 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$51,018,000	$48,237,000	$50,159,000
Section 205 Procurement reduction....................	---	-19,000	---
Section 207 SLUC reduction......	---	-1,000	---
Section 513 S&E reduction.......	---	-37,000	---
Subtotal, adjusted appropriation..............	51,018,000	48,180,000	50,159,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities........	-4,229,000	---	---
Subtotal, adjusted budget authority...........	46,789,000	48,180,000	50,159,000
Unobligated balance, lapsing....................	- 16,000	---	---
Total obligations..........	46,773,000	48,180,000	50,159,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1994--$2,624,000; FY 1995--$6,650,000; FY 1996--$6,650,000.

Also excludes funding for HIV activities: FY 1995--$4,577,000; FY 1996--$4,896,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting..............	113	$24,453,000	102	$23,398,000	100	$24,322,000
Admin. supplemental.......	(14)	360,000	(15)	415,000	(15)	432,000
Competing						
Renewal.................	4	1,454,000	5	1,763,000	6	2,237,000
New.....................	33	6,279,000	37	7,614,000	37	7,785,000
Supplemental...........	--	---	--	---	--	---
Subtotal, competing............	37	7,733,000	42	9,377,000	43	10,022,000
SBIR/STTR	3	641,000	4	912,000	4	950,000
Subtotal, res. proj.........	153	33,187,000	148	34,102,000	147	35,726,000
Research Centers............	8	1,799,000	7	1,873,000	7	1,873,000
Other Research						
Research career program...	15	1,089,000	14	1,247,000	14	1,284,000
Coop. Clin................	---	150,000	---	154,000	---	158,000
Other research related....	9	706,000	8	501,000	8	516,000
Subtotal, other research	24	1,945,000	22	1,902,000	22	1,958,000
Total, research grants........	185	36,931,000	177	37,877,000	176	39,557,000

Training:						
Individual awards:						
Noncompeting	71	999,000	80	1,242,000	78	1,270,000
Competing	23	345,000	26	429,000	28	442,000
Subtotal, individual	94	1,344,000	106	1,671,000	106	1,712,000
Institutional awards:						
Noncompeting	99	2,465,000	85	2,272,000	86	2,362,000
Competing	9	219,000	8	202,000	7	192,000
Subtotal, institutional	108	2,684,000	93	2,474,000	93	2,554,000
Total, training	202	4,028,000	199	4,145,00	199	4,266,000
Research and development contracts	2	568,000	3	848,000	3	848,000
	FTE		FTE		FTE	
Intramural research	9	641,000	9	622,000	9	644,000
Research management and support	44	4,621,000	41	4,688,000	41	4,844,000
Total	53	46,789,000	50	48,180,000	50	50,159,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Summary of Changes

1995 Estimated budget authority	$48,180,000
1996 Estimated budget authority	$50,159,000
Net change	+$1,979,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural				
a. Within-grade increases		$282,000		+$4,000
b. Annualization of January 1995 pay increases		282,000		+2,000
c. One more day of pay		282,000		+1,000
d. January 1996 pay increase		282,000		+5,000
e. Payment for centrally furnished services		53,000		+18,000
f. Increased cost of laboratory supplies, materials and other expenses		287,000		+9,000
Subtotal				+39,000
2. Research Management and Support				
a. Within-grade increases		2,532,000		+37,000
b. One more day of pay		2,532,000		+10,000
c. Annualization of January 1995 pay increases		2,532,000		+21,000
d. January 1996 pay increase		2,532,000		+43,000
e. DHHS Working Capital Fund		53,000		-1,000
f. Payment for centrally furnished services		870,000		+160,000
g. Service and supply fund increase		180,000		+6,000
h. Increased cost of supplies, materials and other expenses		1,026,000		+29,000
i. Reduction for FTS 2000		27,000		-4,000
Subtotal				+301,000

Summary of Changes--continued

B. Program:	No.	Amount	No.	Amount
1. Research projects grants:				
a. Noncompeting................	102	23,398,000	-2	+924,000
b. Admin supplements...........	(15)	415,000	---	+17,000
c. Competing................	42	9,377,000	+1	+645,000
Subtotal...............	144	33,190,000	-1	+1,586,000
d. SBIR/STTR	4	912,000	---	+38,000
Total..................	148	34,102,000	-1	+1,624,000
2. Other research..................	22	1,902,000	---	+56,000
3. Research training...............	199	4,145,000	---	+121,000
	FTEs		FTEs	
4. Intramural research.............	9	622,000	---	-17,000
5. Research management and support.	41	4,688,000	---	-145,000
Subtotal.......................			---	+1,639,000
Total changes..........				+1,979,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	50	50	---
Full-time equivalent of overtime and holiday hours................	0	0	---
Average ES salary....................	$101,800	$101,800	---
Average GM/GS grade..................	11.2	11.2	---
Average GM/GS salary.................	$51,340	$52,470	+$1,130
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$65,072	$65,072	---
Average salary of ungraded positions.	$57,877	$59,150	+$1,273
Personnel compensation:			
Full-time permanent.................	$1,988,000	$2,126,000	+$138,000
Other than full-time permanent......	284,000	296,000	+12,000
Other personnel compensation........	15,000	16,000	+1,000
Subtotal, personnel compensation.	2,287,000	2,438,000	+151,000
Personnel benefits..................	527,000	549,000	+22,000
Travel and transportation of persons	83,000	86,000	+3,000
Transportation of things............	15,000	23,000	+8,000
Rent, communications and utilities..	76,000	79,000	+3,000
Printing and reproduction...........	94,000	97,000	+3,000
Other services:			
Consulting services...............	119,000	123,000	+4,000
Project contracts.................	848,000	848,000	---

	1995 Appropriation	1996 Estimate	Increase or Decrease
Other services....................	116,000	120,000	+4,000
Purchases of goods and services from Government Accounts........	1,800,000	1,773,000	-27,000
Supplies and materials.............	53,000	55,000	+2,000
Equipment..........................	126,000	130,000	+4,000
Insurance Claims and Indemnities...	14,000	15,000	+1,000
Grants, subsidies and contributions....................	42,022,000	43,823,000	+1,801,000
Total budget authority by object......................	48,180,000	50,159,000	+1,979,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)...........	$1,988,000	$2,126,000	+$138,000
Other than Full-Time Permanent (11.3).	284,000	296,000	+12,000
Other Personnel Compensation (11.5)...	15,000	16,000	+1,000
Total Personnel Compensation (11.9).	2,287,000	2,438,000	+151,000
Civilian Personnel Benefits (12.1)......	527,000	549,000	+22,000
Benefits to Former Personnel (13.0).....	---	---	---
Travel (21.0).........................	83,000	86,000	+3,000
Transportation of Things (22.0).........	15,000	23,000	+8,000
Rental Payments to Others (23.2)........	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3)..........	76,000	79,000	+3,000
Printing and Reproduction (24.0)........	94,000	97,000	+3,000
Consulting Services (25.1).............	119,000	123,000	+4,000
Other Services (25.2)..................	116,000	120,000	+4,000
Purchase of goods and services from Government Accounts (25.3)......	1,800,000	1,773,000	-27,000
Operation of GOCOs (25.4)...............	---	---	---
Supplies and Material (26.0)............	53,000	55,000	+2,000
Total............................	5,170,000	5,343,000	+173,000

National Institutes of Health

National Institute of Nursing Research

Significant Items in the Senate Appropriations Committee Report

Item	Action Taken or To be Taken
1995 Senate Report	
Health Promotion/Disease Prevention	
1. The Senate in its report 103-318, page 99, stated: "...The Committee urges the NINR to continue to build on its health promotion studies with adolescents to include young children, in order to discover what motivates risk-taking behavior, and which corrective interventions are best to encourage or substitute healthy behavior.	1. The NINR has collaborated with NHLBI on a program announcement released in the October 28, 1994, issue of the NIH Guide: "Physical Activity and Cardiopulmonary Health." The specific interest of the NINR in this program announcement is in research related to further understanding the dose/response rate of physical activity patterns among younger children and effective interventions for the early establishment of healthy exercise habits among school-aged children. Program development efforts will target those investigators currently involved in school-based health programs.
Women's Health	
2. The Senate in its report 103-318, page 100, stated: "...The Committee urges the NINR to work with the National Cancer Institute to mount research studies addressing breast cancer, including symptom management, quality of life issues, and preventive screening.	2. Through the Interagency Working Group on Breast and Gynecologic Cancer, program staff are exploring possible collaborative opportunities with NCI on research related to breast cancer. The NINR is assigned dual consideration for funding with NCI and will seek shared funding opportunities for pending research applications related to psychosocial adjustment and symptom management during breast cancer treatment.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amt. Authorized	1995 Appropriation	1996 Amt. Authorized	1996 Budget Request
Research and Investigation......	Section 301	42§241	Indefinite	$44,035,000	Indefinite	$45,893,000
National Institute of Nursing Research......................	Title IV, Part C	42§285q	Such sums as necessary		Such sums as necessary	
National Research Service Awards......................	Section 487(d)	42§288	Such sums as necessary	4,145,000	Such sums as necessary	4,266,000
Total Budget Authority.......				48,180,000		50,159,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	---	$16,700,000	$20,000,000	$20,000,000
1988	16,133,000	24,744,000 2/	23,566,000	23,380,000
1989	24,400,000 3/	27,417,000 4/	28,107,000	29,139,000
1990	29,970,000 5/	32,969,000	34,969,000	33,935,000 6/
1990 Sequester				-422,000
1991	35,127,000	37,289,000 7/	40,013,000	39,722,000 8/
1991 Sequester				-1,000
1992	43,747,000	43,143,000	45,880,000	44,970,000 9/
1993	48,568,000	47,363,000	49,000,000	48,119,000 10/
1994	48,975,000	51,018,000	51,018,000	51,018,000
1995 11/	48,326,000	47,971,000	48,326,000	48,180,000 12/
1996 11/	50,159,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research consolidated at the Secretary's level.

3/ The 1989 request excludes funds for AIDS research and education ($707,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes $2,690,000 in NRSA training programs not considered.

5/ The 1990 request excludes funds for the National HIV Program ($999,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of $34,000.

7/ Excludes $4,233,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of $1,046,000.

9/ Excludes enacted administrative reductions of $226,000.

10/ Excludes enacted administrative reductions of $472,000.

11/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

12/ Excludes enacted administrative reductions of $19,000, $1,000, & $37,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Nursing research...	--	$37,811	--	$40,476	--	$41,527	--	$42,870	--	$44,671	--	$+1,801
Intramural research..	7	198	9	373	9	630	9	622	9	644	--	+22
Research management and support........	41	4,206	43	4,662	44	4,616	41	4,688	41	4,844	--	+156
Subtotal, obligations	48	42,215	52	45,511	53	46,773	50	48,180	50	50,159	--	+1,979
Unobligated balance lapsing...........		4		19		16		---		---		---
Total budget authority........	48	42,219	52	45,530	53	46,789	50	48,180	50	50,159	--	+1,979

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Nursing Research

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
53	$46,789,000	50	$48,180,000	50	$50,159,000	--	+$1,979,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute of Nursing Research. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute of Nursing Research (NINR) supports biomedical and behavioral research and research training programs to reduce the burden of illness and disability for individuals and their families, improve the quality of life and establish better means to promote health and prevent disease, and reduce the costs of care. These research programs address symptoms and side-effects of disease and treatment; health behaviors and health habits, including those that interact with heritable diseases; and models to improve patient care and the environment in which it is delivered.

Maintaining and improving quality of care while reducing health care costs is a major focus of nursing research. One recently confirmed approach to reduced costs and improved treatment outcomes is transitional home follow-up care, a model of care designed to shorten patients' hospital stays by replacing a portion of hospital care with a comprehensive program of home follow-up by nurse specialists. The cost-effectiveness of this model has been demonstrated in a transitional program for women hospitalized with a variety of medical problems. Now, a study of older people hospitalized for nonsurgical cardiac treatments has shown that discharge planning and telephone follow-up have reduced readmissions and increased the time between hospitalizations, reduced the number of in-patient days following readmission, and lowered costs for rehospitalization by 60% at four weeks.

In FY 1996, NINR's extramural and intramural programs will continue to emphasize research that will eliminate or diminish the societal impact of disease, disability, and recovery from illness, as described below.

Pain is a critical, common, and costly health problem that can result in severe, sometimes unrelieved unbearable discomfort, with consequent loss of productivity and poor quality of life. Research indicates that pain may be life-threatening and can affect the immune and endocrine systems. Pain and its treatment can cause other problems, such as loss of appetite, immobility, and sleep loss, that affect physical well-being and quality of life. Research at the cellular and molecular levels is key to understanding the neural mechanisms that cause pain and that can be altered to reduce or eliminate it. Nursing research builds from this basic research to test interventions to prevent, reduce the occurrence of, and alleviate pain in persons of all ages. In collaborative efforts with other ICDs, in FY 1996, NINR will emphasize neurobiological pain research.

Americans are living to older ages, due in part to dramatic advances in the identification and elimination of environmental hazards and the treatment of acute illness. However, little progress has been made in postponing and treating nonfatal, chronic illnesses such as sensory impairments, degenerative neurological diseases, and musculoskeletal diseases. These conditions have major implications for societal burdens and costs. Dementia, primarily due to Alzheimer's disease and strokes, causes severe dependency and disability. According to a report published by the National Institute on Aging in 1993 (Progress Report on Alzheimer's Disease, 1993, National Institute on Aging, National Institutes of Health), an estimated 4 million Americans suffer from Alzheimer's disease, which costs the Nation an estimated $90 billion per year, including medical bills, nursing home costs, home care costs, and lost productivity. Basic research is vital to identifying etiologies and treatments for this and other chronic, progressively disabling conditions. However, until cures are developed, attention must also be paid to preserving the functioning and well-being of elderly Americans as long as possible. NINR will continue collaborative research efforts in the management of cognitive, behavioral, and physical symptoms that will reduce the emotional, physical, and economic costs of this disease for patients and their families.

Health behaviors assumed in early childhood can have substantial health consequences in adulthood. Research has shown that by adolescence, opinions and attitudes about such health compromising behaviors as drinking alcohol, smoking, poor nutritional habits, and taking chances with personal safety are already well established. In FY 1996, the NINR will continue to support research to understand how health habits and behaviors are developed in the early years, how unhealthy habits and risky behaviors can be changed, and how these changes can be maintained throughout the life span. Other research questions include when, how, and with what frequency interventions should be undertaken to assure the best chance of success in promoting health.

Because heritable diseases affect a significant proportion of the population, the potential benefits associated with early detection and intervention are substantial. Thus, as molecular genetics evolves, genetic diagnoses, testing and treatment will be launched into the mainstream of health care practice. Research programs are required to examine interactions among genetic predisposition, environment, and life style. In FY 1996, the NINR intramural program will examine the clinical implications of genetic testing with a focus on inborn risks and interactions of those risks with lifestyles and health habits and behaviors in culturally diverse populations. Other research will focus on decision-making processes associated with implementation of gene therapy, as well as the physiological, psychosocial, and economic effects of gene therapy on individuals and their family.

Disease-causing microbes have threatened human health for centuries. Modern drugs, vaccines, and pesticides are important weapons in controlling pathogens, but the use of these very weapons has contributed to mutations, adaptations, and migrations that have enabled organisms to further proliferate or acquire virulence. Complacency about prevention and treatment of infectious diseases has further compounded this situation. Health professionals are less vigilant, and infected or at-risk individuals are not as motivated to adhere to recommended behavior changes or medical treatment regimens. NINR will offer opportunities for nurse researchers to develop and test strategies to reach hard-to-engage populations most at risk for contracting and spreading emerging infections such as AIDS and tuberculosis.

Research has shown that minority and underserved populations experience higher prevalences of many diseases and conditions. This higher prevalence has been attributed to problems in accessibility, affordability, and acceptability of health-care delivery systems. These problems are especially severe in rural locations. Research sponsored by NINR will evaluate health outcomes for persons participating in community-based health-care programs and determine program features that are essential to the delivery of effective care. Attention will focus primarily on the unique cultural requirements of minorities and underserved populations in rural areas and how models of care affect health outcomes, burden of illness, and costs of care in these population groups.

The President's appropriation request of $50,159,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Nursing Research during the last 5 years has been as follows:

Year	Amount	FTE's
FY 1991	$37,364,000	39
FY 1992	42,219,000	48
FY 1993	45,530,000	52
FY 1994	46,789,000	53
FY 1995	48,180,000	50

Purpose and Method of Operations

The National Institute of Nursing Research supports a number of important research efforts. The NINR Extramural Research Program supports research on the prevention and management of symptoms associated with a specific disease, such as Alzheimer's disease; HIV/AIDs; tuberculosis and other infectious diseases; cancer, with a focus on breast cancer; cardiovascular disease; diabetes; and musculoskeletal disorders. It also targets specific symptoms that may occur in a number of diseases. Such symptoms include pain, fatigue, cognitive difficulties, wasting and nutritional disturbances, sleep disorders, respiratory distress, urinary incontinence, and the effects of major trauma.

Another major area of research is that of health promotion and disease prevention. Health promotion and disease prevention questions span the life course and encompass many diseases and disabilities. NINR supports research on the prevention of low birth weight, midlife symptoms experienced by women, and issues that are unique to older people and their caregivers. Questions in health promotion address such issues as weight maintenance and nutrition, exercise and appropriate physical activity levels, sleep and rest patterns, and modification of risky behaviors in young people.

Research on clinical care encompasses investigations about the best setting for care delivery for the patient and how decisions about appropriate clinical care are made in uncertain or complex diagnostic and treatment situations. In research about clinical care, the issues of culture, ethnicity, and race are paramount. These investigations focus on how medical and nursing care is provided to patients and their families for improved outcomes. Bioethical questions are also under study.

Overall Budget Policy

The FY 1996 budget request for the NINR is $50,159,000. This amount represents an increase of $1,979,000, or 4.1 percent over the comparable FY 1995 level. This level of funding will enable the Institute to maintain its ongoing nursing research programs, particularly in the areas of the neurobiology of pain, management of symptoms associated with Alzheimer's disease, establishment of healthy behaviors in younger children, decision-making related to genetic testing and therapy, adherence to treatment for HIV infection and AIDS, and community-based programs for minority and underserved populations in rural areas. In addition, this increase will provide funds for expansion of research initiatives in the areas of breast cancer, prevention research, and diseases related to bone, muscle and connective tissue.

The FY 1996 budget request for research project grants is $35,726,000. This level will support a total of 147 research project grants: 100 noncompeting research project grants, as compared to 102 in FY 1995; and 43 competing research project grants, as compared to 42 in FY 1995. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment. Within the competing component, average grant awards received an increase approximately equal to the biomedical research and development price index.

In research centers, the request provides $1,873,000, the same level as in FY 1995, to continue funding seven research centers.

The FY 1996 request includes $1,958,000 for the other research grants mechanism which maintains the same number of awards as in FY 1995. This allows continued funding for 14 research career awards, support for a cooperative clinical trial in collaboration with the National Eye Institute, and funding for 8 other research grants.

In research training, the amount requested is $4,266,000, which will allow funding for 199 full-time training positions, the same number funded in FY 1995.

The amount requested for research and development contracts is $848,000 for 3 awards, also the same level as FY 1995.

The FY 1996 request provides $644,000 and 9 FTE's for intramural research, as compared to $622,000 and 9 FTE's in FY 1995.

In research management and support, the FY 1996 request provides $4,844,000 and 41 FTE's, as compared to $4,688,000 and 41 FTE's in FY 1995. This amount will cover a portion of the increases for centrally furnished services, pay-related costs, and other supplies, equipment, and services.

National Institute of Nursing Research

Extramural Research

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$41,527,000	$42,870,000	$44,671,000	+$1,801,000

Funding for the Nursing Research activity during the last 5 years has been as follows:

Year	Amount
FY 1991	$33,731,000
FY 1992	37,811,000
FY 1993	40,476,000
FY 1994	41,527,000
FY 1995	42,870,000

Rationale for the Budget Request

The FY 1996 budget request for Extramural Research is $44,671,000, as compared to the FY 1995 estimate of $42,870,000. Developed on the scientific bases of current research in their respective programs, the following are samples of research activities that will be supported through the Extramural Research Program in FY 1996.

The Neurobiology of the Pain Experience

Pain is a critical and prevalent health problem. In addition to possible deleterious effects on immune function, pain can significantly affect quality of life and cause disruptions in sleep, eating, mobility, and general functional status. For hospitalized patients, pain may be associated with longer stays, delayed recovery, and poorer patient outcomes, which all have implications for patients' well-being and for the quality and costs of health care. In FY 1996, NINR will extend its research program to neurobiological aspects of pain, in collaboration with several other NIH institutes and centers. A major goal of this research is to be able to prevent chronic pain. Investigators will address the following kinds of issues: the neurochemical basis of pain perception and the discovery of targets in the signal transduction pathways as the most effective point for interventions in the control of pain; discovery of compounds that mimic the effect of endogenous analgesic systems; systematic studies of the efficacy of pharmacological and behavioral approaches to the control, management and alleviation of pain; the molecular mechanisms of pain modulation and control by such variables as genetics, neuroendocrine and neuroimmune changes; and refinement of neuroimaging algorithms for the study of structural and functional correlates of pain perception. Among all the sensory systems which have a profound effect on quality of human life, the sense of pain is the most complex and least understood.

Management of Behavioral Symptoms of Alzheimer's Disease

While the average life span continues to increase, little progress has been made in the prevention and treatment of a number of debilitating diseases of later life. These diseases, such as Alzheimer's disease, are very costly to our society. Nursing research identifies ways to adapt the environment to the needs of older patients, their families, and their caregivers so that independence can be prolonged through improved functional status.

The progression of Alzheimer's disease is characterized by a series of cognitive and behavioral symptoms. Cognitive failures such as memory lapses and spatial disorientation occur in the early stages of the disease. In the middle stages, behavioral symptoms become prominent. These symptoms, which include wandering, aggressive behavior, disrupted sleep, pacing and agitation, difficulty dressing, toileting problems, and incontinence, can become very difficult to manage and often result in decisions to institutionalize patients, with the resulting high costs of nursing home care.

Investigations supported by NINR address the following types of questions: What factors lead to specific behavioral problems? What is the relationship between these behaviors and advancing neurological damage? In addition to neurological and motor changes, what behavioral and environmental factors contribute to urinary incontinence? Trials will be conducted to test interventions for specific symptoms such as nocturnal sleep-wake patterns, wandering, screaming, and other disruptive vocalizations. Research is also needed to develop clinical interventions that maintain cognitive and physical functioning and forestall end-stage manifestations of the disease, which include confinement to bed, inability to communicate, incontinence, and contractures and pressure ulcers. Nursing research also focuses on the care for these individuals and their families.

Establishing Healthy Behaviors in Younger Children

The NINR is supporting research regarding the development of poor health habits and risky behaviors, which can compromise health and quality of life, lead to premature death, and add tremendous costs to the health-care system. Health-related practices in the early years have a significant impact on health throughout the life course. For example, it is well known that many common health problems of adulthood, such as heart disease, high blood pressure, noninsulin-dependent diabetes, osteoporosis, and obesity, have links to unhealthy behaviors learned in the early years. Similarly, diet and exercise habits, responses to stressful situations, and tendencies to take risks are behaviors formed in childhood. Therefore, interventions need to be targeted to an earlier age to encourage the adoption of lifelong healthy and safe behaviors. In FY 1996, the NINR will continue to support research on how health behaviors are formed during the critical developmental period of early childhood, how these behaviors can be changed, and how the changes can be maintained across the life span. The implementation of interventions in terms of timing, content, and frequency will also be examined.

Genetics

The evolution in molecular genetics has resulted in rapid technological advances that are far outpacing our knowledge about the clinical application of this technology. Successful outcomes from genetic diagnoses, testing, and treatment will depend on understanding the interactions among genetic predisposition, environment, and lifestyle; the impact of genetic testing and associated decision-making; the long-term impact of genetic therapies; and the ethical aspects of genetic testing and intervention. NINR will support intramural and extramural research, some in collaboration with the National Center for Human Genome Research, to examine the impact of genetic testing and related issues on individuals and their families. The following types of questions will be investigated: What types of factors should be considered in decisions about genetic testing and who should be involved in the decision-making process? What special considerations must be considered in making decisions for children and nonautonomous adults? How can cultural differences be incorporated in this process? What counseling and teaching strategies will provide the most assistance in the decision process? How can individual privacy be protected as increasing amounts of genetic information becomes available? What is the economic impact of genetic testing and the genetic therapies?

Emerging Infections

Failure to complete recommended treatment or adhere to recommended health behaviors accounts for a significant part of the health-care burden facing our nation. For example, failure to complete recommended treatment by infected but symptom-free tuberculosis patients has contributed to a rapid rise in the number of tuberculosis cases over the past four years. Partially or untreated patients continue to infect others in community facilities, long-term care institutions, and prisons. In addition, lack of adherence to treatment regimens has resulted in an increased number of cases for which current drug therapies are not effective. Building on earlier initiatives with other Federal agencies to address the complex problems involved in adherence to tuberculosis treatment, in FY 1996, NINR will place increased emphasis on interventions that address personal, social, and cultural barriers to adherence with prevention and treatment regimens, with special attention to populations that are difficult to treat and monitor.

Health of Minority and Underserved Populations in Rural Settings

There are indications that subpopulation groups identifiable by geography and/or cultural affiliation encounter unique barriers to health care. Community-based health-care programs that focus on specific population groups have not been scientifically evaluated. In FY 1996, NINR will support evaluation of models for comprehensive community-based health-care programs for minorities and other underserved groups in rural communities. The premise underlying this research is that better understanding of the special needs of minority populations will improve the outcomes of prevention and treatment measures provided by these programs.

Nursing research has shown that when cultural factors unique to specific populations are included in the design of community-based health-care programs, participation rises, use of certain interventions or treatments increases, and risk factors are detected earlier. Research has also shown that understanding lifestyles and unique needs of a community is essential to successful collaboration between health-care providers and members of minority and other groups in diverse community settings.

The following are some of the research questions that require attention: What are the most effective ways of obtaining community participation in the planning, design, and implementation of preventive programs? To what extent are differences among subpopulations in the acceptance of preventive strategies culturally driven and how can these differences best be accommodated in prevention programs? How do comprehensive community-based prevention programs compare with traditional episodic primary care programs in terms of patient outcomes such as health status, risk factors, clinical factors, and cost features?

Breast Cancer

Breast cancer is the most common cancer among women in the United States. The NINR is developing a portfolio of research on screening and detection and the management of symptoms and problems that result from surgical and chemotherapeutic treatment of breast cancer. While it is widely documented that screening measures such as breast self-examination and mammography are very valuable in early detection and cure, understanding of and compliance with these measures vary dramatically by population and subpopulation groups of women. If we are to improve screening rates and the acceptance of various treatments (which will ultimately improve mortality rates), interventions to reinforce adherence and compliance with screening and treatment must include culturally specific features. NINR will continue its cooperation with the National Cancer Institute in supporting research on these important issues.

Musculoskeletal Disorders

Many of these disorders, which are associated with advancing age, are addressed by nursing research programs. Falls and hip fractures, often occurring in conjunction with osteoporosis and arthritis, present chronic, confining, and costly problems for older people and those who assist them. NINR will continue to encourage investigations that address symptom management and improved physical functioning in people with common musculoskeletal disorders.

National Institute of Nursing Research

Intramural Research Program

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
9	$641,000	9	$622,000	9	$644,000	--	+$22,000

The Division of Intramural Research comprises two laboratories--the Clinical Therapeutics Laboratory (CTL) and the Laboratory for the Study of Human Responses to Health and Illness (HRHI). The CTL conducts research on the biophysiologic and behavioral bases for and the effectiveness of interventions for nursing practice and health care. CTL projects focus on prevention and treatment of symptoms or side effects that occur as a result of disease, such as HIV infection; injuries; and other health conditions, such as aging.

The HRHI conducts research that focuses on the biophysiologic and behavioral aspects of human responses that occur in health and illness, including processes, mechanisms, and environments that influence health, health-promoting, and health- maintaining behaviors; interventions that reduce the risk of illness; and interventions that facilitate adaptation to illness or disability.

Funding for the Intramural Research activity during the last 5 years has been as follows:

Year	Amount	FTE's
FY 1991	$150,000	5
FY 1992	198,000	7
FY 1993	392,000	9
FY 1994	641,000	9
FY 1995	622,000	9

Rationale for the Budget Request

The FY 1996 request for intramural research is $644,000 as compared to the FY 1995 estimate of $622,000. The following are examples of current and planned program activities within the Intramural Research Program.

The CTL is conducting research related to older Americans, focusing on chronic symptoms in elderly women. In one study, the combined effects of estrogen therapy and pelvic muscle exercise are being assessed in the treatment of incontinence and the distressing urinary symptoms of urgency and frequency in community-dwelling postmenopausal women. In another study, an intervention is being implemented in post-hip fracture patients in an acute care setting to prevent incontinence and reduce postoperative urinary complications, such as urinary tract infections and incomplete bladder emptying, and to reduce the risk of institutionalization of the older adult.

The CTL also is developing a program of research on clinical ethics. The research will focus on decision-making about participating in genetic testing studies and/or clinical trials, such as vaccine testing, and the effects of such decisions on the individuals and their families. These studies will also identify factors that influence individuals' willingness to participate in these studies. The ethical issues related to informed consent (including consent for children and vulnerable populations) will be investigated. Interventions that facilitate effective decision-making for individuals and families will then be developed.

The HRHI staff has undertaken investigations to improve the quality of life for individuals and families engaged in health-promoting/risk-reducing behaviors and/or living with a chronic illness, as well as interventions that facilitate adaptation in illness or disability. Studies currently in progress include a study, in collaboration with the National Heart, Lung, and Blood Institute and the National Institute on Aging, of caregiving, health, and quality of life in women who care for aging men with dementia. The effects of the long-term care burden on the immune system of caregivers is being investigated, as well as factors that promote successful adjustment following the death of the dementia patient.

Another study focuses on the role of functional status in persons with chronic illnesses. An easy-to-wear mechanical device that measures activity is being tested in order to assess functional performance accurately and compare activities with subjective reports of performance. This will enable investigators to evaluate functional status more accurately as an outcome of chronic illness and, ultimately, to develop interventions aimed at improving functional status so that individuals can maintain their independence as long as possible.

National Institute of Nursing Research

Research Management and Support

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
44	$4,621,000	41	$4,688,000	41	$4,844,000	--	+$156,000

The Research Management and Support (RMS) activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: the Office of the Director, the Office of Administrative Management, the Office of Planning, Analysis, and Evaluation, and the Office of Information and Legislative Analysis. Also included in the RMS activity are the staff of the Division of Extramural Programs, who are responsible for providing scientific direction, review, and program management for the Institute's extramural scientific portfolio.

Funding for the RMS Activity during the past five years has been as follows:

Year	Amount	FTE's
FY 1991	$3,483,000	34
FY 1992	4,210,000	41
FY 1993	4,662,000	43
FY 1994	4,621,000	44
FY 1995	4,688,000	41

Rationale for the Budget Request

The FY 1996 request for RMS is $4,844,000, as compared to the FY 1995 estimate of $4,688,000. This amount will cover a portion of the increases for centrally furnished services, pay-related costs, and other supplies, equipment, and services. Efforts will continue to carefully examine and streamline work processes and procedures wherever possible in order to reduce costs and improve efficiency in conjunction with the Administration's efforts to reinvent Government.

This activity provides the program guidance, planning and evaluation, leadership, and overall administration for all programs of the Institute, and conducts a broad program of information dissemination directed toward the public, practitioners in nursing, and other health professionals. Direct support is also provided for the continuing development and coordination of the National Nursing Research Agenda.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director........	4	3	3
Office of Scientific Review...	6	5	5
Office of Planning, Analysis and Evaluation..............	6	6	6
Office of Information and Legislative Analysis........	4	4	4
Office of Administrative Management.................	11	10	10
Division of Extramural Research...................	13	13	13
Division of Intramural Research...................	9	9	9
Total, NINR	53	50	50

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1991.........................	10.6
1992.........................	10.7
1993.........................	11.1
1994.........................	11.2
1995.........................	11.2
1996.........................	11.2

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-3	---	1	1
ES-2	---	---	---
ES-1	---	---	---
Subtotal	---	1	1
Total - ES Salary	---	$101,800	$101,800
GM/GS-15	7	7	7
GM/GS-14	5	5	5
GM/GS-13	6	6	6
GS-12	6	6	6
GS-11	3	3	3
GS-10	1	1	1
GS-9	1	1	1
GS-8	4	5	5
GS-7	5	4	5
GS-6	3	3	2
GS-5	1	1	1
GS-4	2	2	2
GS-3	---	---	---
GS-2	1	1	1
GS-1	---	---	---
Subtotal	45	45	45
Grades established by Act of July 1, 1944 (42 U.S.C 207):			
Director Grade	1	1	1
Senior Grade	1	1	1
Subtotal	2	2	2
Ungraded	2	2	2
Total permanent positions	44	45	45
Total positions, end of year	49	50	50
Total full-time equivalent (FTE) employment, end of year	53	50	50
Average ES level	---	3.0	3.0
Average ES salary	---	$101,800	$101,800
Average GS/GM grade	11.2	11.2	11.2
Average GS/GM salary	$49,160	$51,340	$52,470

WEDNESDAY, MARCH 22, 1995.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

WITNESSES

DR. ENOCH GORDIS, DIRECTOR
MARTIN K. TRUSTY, EXECUTIVE OFFICER
STEPHEN LONG, DIRECTOR, OFFICE OF POLICY ANALYSIS
CARMEN M. RICHARDSON, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. We continue our hearings on the National Institutes of Health with the National Institute on Alcohol Abuse and Alcoholism. And we're pleased to welcome Dr. Enoch Gordis, the Director. Dr. Gordis, it's good to see you again. Why don't you introduce the people at the table with you and proceed.

INTRODUCTION OF WITNESSES

Dr. GORDIS. Thank you very much, Mr. Porter.

Sitting on my left here is Mr. Stephen Long, the Director of our Office of Policy Analysis. Sitting on my immediate left is Mr. Martin Trusty, our Executive Officer. On my right is Carmen Richardson, our Budget Officer.

Mr. PORTER. Thank you.

OPENING STATEMENT

Dr. GORDIS. It is a pleasure to be here today to highlight the research advances and future plans of the National Institute on Alcohol Abuse and Alcoholism. The Institute's mission is to focus the Federal Government's endeavors to develop knowledge and promote strategies to prevent and reduce the serious health, social and economic consequences of alcohol abuse and alcoholism in this Nation.

Alcohol misuse accounts for about a hundred thousand deaths in this country each year. It accounts for more economic and social damage than almost any other public health problem. That misuse extracts approximately $98 billion a year in morbidity, mortality and economic vitality, as cited by Professor Dorothy Rice in the "Economic Costs of Alcohol and Drug Abuse and Mental Illness," published in 1990.

About 14 million Americans, almost 8 percent of adults, meet diagnostic criteria for alcohol abuse or alcoholism. The consequences of chronic and heavy drinking include liver disease and pancreatitis. Chronic drinking also contributes to cardiovascular disorders, certain cancers and immune, endocrine and reproductive system illnesses.

Almost half of the highway deaths in this country are attributable to alcohol. The NIAAA estimates that 20 to 40 percent of all persons in urban hospital beds have alcohol problems, regardless of the conditions which initiated their hospitalizations. Although alcohol abuse and alcoholism impose economic consequences of approximately $98 billion annually, only $10.5 billion of this is devoted directly to treatment for alcoholism, alcohol abuse and the subsequent medical complications.

In a number of ways, NIAAA researchers are unraveling the brain chemistry underlying alcohol abuse and alcoholism. They continue to focus on ways to clarify how both vulnerability to alcohol abuse and the effects of chronic alcohol consumption are encrypted in brain chemistry. At the molecular level, a picture is emerging of how craving reflects experience superimposed on vulnerability. This can provide valuable insights for prevention and treatment.

The key to understanding the development of alcohol addiction rests with uncovering the molecular actions of alcohol on neurotransmitter receptors, ion channels, signal transduction systems, and enzymes as they relate to addiction, tolerance and physical dependence. NIAAA scientists are exploring the contribution of genetics, neurobiological and environmental factors leading to uncontrolled drinking.

Using animal models, researchers have demonstrated a genetic influence in a number of areas such as alcohol-seeking behavior, acute sensitivity to alcohol, rate at which alcohol is metabolized, chronic tolerance, physical dependence, and susceptibility to withdrawal seizures. Clearly, however, there is no one gene at the root of alcoholism. NIAAA researchers are looking for phenotypic and genetic markers of vulnerability that would facilitate comprehension of the underlying physiology of alcoholism as a basis for prevention and new medical treatment.

Neuroscience has revealed the role of different neurotransmitter systems in the phenomenon of alcoholism and the effect of alcohol in turn on various neurotransmitter systems. If the brain chemistry of vulnerable individuals enhances the sensation of reward from alcohol, then scientists concluded that it might be possible, using medical means, to short-circuit the craving that results and that drives chronic over-consumption in these individuals. The most promising current efforts involve studies of Naltrexone, an opiate antagonist. Thus, the first new medication in 47 years to treat alcoholism, Naltrexone, was approved by the U.S. FDA in December of 1994.

Naltrexone works by reducing the craving for alcohol and the reinforcing effects of alcohol, thereby increasing abstinence and reducing the rate of severe relapse. When combined with other interventions, in one study Naltrexone allowed as many as three-quarters of alcoholics to avoid a severe relapse, compared with fewer than half of those who received counseling alone.

In conclusion, today we are entering a new era in alcohol research. We are developing priceless new knowledge in the fields of genetics, medications development and the neurosciences that will help us improve the effectiveness of the Nation's prevention and treatment efforts. The first 25 years of research are now producing results in treatment and prevention which stem from basic science. We are finally beginning to understand why for some individuals, alcohol becomes the dominant and destructive force in their lives.

Mr. Chairman, the fiscal year 1996 request for NIAAA is $185,712,000. And we'll be pleased to answer any questions.

[The prepared statement and biography of Dr. Enoch Gordis follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute on Alcohol Abuse and Alcoholism
Statement of the Director

Thank you, Mr. Chairman. It is a pleasure to be here today to highlight the research advances and future plans of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The NIAAA's mission is to focus the Federal government's endeavors to develop knowledge and promote strategies needed to prevent and reduce the serious health, social and economic consequences of alcohol abuse and alcoholism in the United States. Alcohol's misuse accounts for more economic and social damage than almost any other public health problem. That misuse extracts approximately $98.6 billion a year in morbidity, mortality, and economic vitality, as cited by Dorothy Rice in the 1990 issue of *The Economic Costs of Alcohol and Drug Abuse and Mental Illness*. About 14 million Americans--almost 10 percent of adults--meet diagnostic criteria for alcohol abuse or alcoholism. Consequences of chronic and heavy drinking include liver disease and pancreatitis; chronic drinking also contributes to cardiovascular disorders, certain cancers, and immune, endocrine, and reproductive system illnesses. The NIAAA estimates that 20 to 40 percent of all persons in urban hospital beds have alcohol problems regardless of the conditions which initiated their hospitalizations. Although alcohol abuse and alcoholism impose economic consequences of approximately $98.6 billion each year, only a fraction, $10.5 billion of this is devoted directly to treatment for alcoholism, alcohol abuse, and subsequent medical consequences. The remainder can be attributed to lost productivity, excess illness, and early death (Dorothy Rice, 1990).

In both human and economic terms, birth defects are a costly result of alcohol abuse and alcoholism. Alcohol is a teratogen capable of inducing congenital defects, growth retardation, learning disabilities, and negative behavioral outcomes. Alcohol's adverse effects on the fetus exist along a continuum, with complete fetal alcohol syndrome (FAS) at one end of the spectrum, and incomplete features of fetal alcohol effects (FAE), including more subtle cognitive-behavioral deficits, on the other. The NIAAA was responsible for the finding that FAS is caused by alcohol per se and for spearheading efforts to alert women and the medical community to the dangers of drinking during pregnancy. NIAAA researchers will continue to develop the scientific basis for prevention and effective intervention for FAS and FAE, with special efforts made on how best to communicate this message to women whose drinking behavior has not been changed by current efforts. Research will be conducted to explore the genetic attributes of the fetus that may contribute to susceptibility to the effects of alcohol. Basic biomedical research will focus on how prenatal exposure to alcohol disrupts normal fetal development, by exploring alcohol's effects on developmental gene regulation and neural cell division.

Today the gap between behavioral and biomedical basic science is rapidly disappearing. Researchers have discovered that it is possible to identify genes that influence complex behavior. These behaviors influence the onset of various diseases, as in cancer (smoking), heart disease, and alcoholism. NIAAA scientists continue to explore not only genetic coding for aspects of behavior, but also the role environmental influences play in determining the manifestation of certain behaviors. In fact, the role of the environment can be more precisely determined when both genetic and environmental factors are studied together. "Environment" includes at least two kinds of influences: influences that affect the actual structure and function of the nervous system, especially in the young, when it is known to be affected by various inputs; and second, influences of home and peers as well as the effect of social and policy decisions regarding access to alcohol and its use. Alcohol research provides useful examples of the importance of the interplay between these approaches and the dividends of such investigation.

In a number of ways, NIAAA researchers are unraveling the brain chemistry underlying alcohol abuse and alcoholism. They continue to focus on ways to clarify how both vulnerability to alcohol abuse and the effects of chronic alcohol consumption are encrypted in brain chemistry. At the molecular level, a picture is emerging of how craving reflects experience superimposed on vulnerability; this can provide valuable insights for prevention and treatment. The key to understanding the development of alcohol addiction rests with uncovering the molecular actions of alcohol on neurotransmitter receptors, ion channels, signal transduction systems, and enzymes as they relate to addiction, tolerance, and physical dependence. NIAAA scientists are exploring the contributions of genetic, neurobiological, and environmental factors leading to uncontrolled drinking. These studies may provide a clearer understanding of the genetic differences that exist among individuals as well as populations. Research is progressing at a rapid pace in both humans and animals. Over the past twenty years, twin and adoption studies and studies of selectively bred animal lines have yielded evidence for genetic transmission of vulnerability for alcoholism. Studies of twins and of the psychology and physiology of alcohol-dependent patients point to an inherited vulnerability to alcohol dependence. Using animal models, researchers have demonstrated a genetic influence in a number of areas such as alcohol-seeking behavior, acute sensitivity, rate at which alcohol is metabolized, chronic tolerance, physical dependence, and susceptibility to withdrawal seizures. Clearly, however, there is no one gene at the root of alcoholism. NIAAA researchers are looking for phenotypic and genetic markers of vulnerability that would increase understanding of the underlying physiology of alcoholism as a basis for prevention and medical treatment.

One such study is the Institute's Collaborative Study of the Genetics of Alcoholism (COGA). Studies of psychiatric genetics present particular difficulties, such as the multigene nature of disorders like alcoholism, incomplete penetrance of the genes involved, and the necessity of an environmental contribution for expression of the phenotype. Recruiting large numbers of patients is one strategy to compensate for these confounding factors. COGA examined 24,000 consecutive admissions to recruit 5,400 individuals from 800 alcoholic families. Diagnostic precision--both for evaluating patients with alcoholism and evaluating the strength of family history--is another difficulty. COGA has generated a state-of-the-art set of diagnostic questions designed to provide a more precise means of diagnostic assessment for research purposes.

COGA scientists have investigated spontaneous electrical activity in the brain (electroencephalograms) and activity following sensory stimuli (evoked response potentials, or ERPs) as possible measures of how brain function is altered in those at risk for alcoholism and by alcohol consumption. The reduced amplitude of one ERP component--designated P300--is an example of a neurophysiologic marker that is reliably associated with risk of alcohol abuse. Ongoing studies are exploring possible parallels between neurophysiologic markers, such as P300, and psychophysiologic markers of risk, such as reduced sensitivity to the intoxicating effects of alcohol, as well as the tendency for alcohol to blunt behavioral and cardiovascular hyperactivity in high-risk subjects. An integrated picture of alcohol's effects on the brain and the behavior of at-risk persons should provide diagnostic clues to vulnerability and a sound basis for exploring the heritability of phenotypic markers.

COGA moves us from the population genetics in informative families to the search for individual genes. This study will provide further information about familial transmission of vulnerability and the interaction of environmental and genetic factors in the expression of alcoholism--data valuable for identifying individuals at risk and designing effective preventive interventions. Clearly defined strains of animals that differ in various reactions to alcohol are now being studied with the Quantitative Trait Loci (QTL) mapping technique which helps us to define the contributions of individual genes to certain complex behaviors. Identification of genes responsible can later serve as a guide to searching the human genome. When scientists can identify the mixtures of environmental and genetic factors that place individuals at risk, society will experience the greatest possible return on investment in alcohol research: the capacity to target accurately our prevention and treatment efforts.

Neuroscience has revealed the role of different neurotransmitter systems in the phenomenon of alcoholism and the effect of alcohol in turn on various neurotransmitter systems. This has led to important new insights into the cellular actions of alcohol. Using cell cultures and animal studies, NIAAA grantees and intramural scientists have revealed that exposure to alcohol induces both acute and chronic changes in levels of a variety of neurotransmitters involved in the sensation of reward, especially in vulnerable individuals. For example, alcohol causes an acute increase in levels of neurotransmitters, such as serotonin, opioids, and dopamine (and in tissue culture, cyclic adenosine monophosphate); in chronic users the base level of these chemicals is lowered, which increases craving and raises the "reward threshold." Scientists now believe that these effects prompt animals and humans to then seek more alcohol to, in effect, self-medicate and bring neurotransmitters up to "normal" levels. Hypothesizing that the risk for alcoholism may be associated in some persons with alterations in the function of the neurotransmitter serotonin, scientists have studied both animals and humans and indeed found abnormal serotonin function in human alcoholism and in specially bred animals with high preference for alcohol. Findings from neuroscience research revealed that the use of medications that interact with the neurotransmitter receptors--involved in the response to alcohol--could serve as adjuncts to treatment for alcoholism. If the brain chemistry of vulnerable individuals enhances the sensation of reward from alcohol, then scientists concluded that it might be possible, using medical means, to short-circuit the craving that results and that drives chronic overconsumption in these individuals. The most promising current efforts involve studies of naltrexone, an opiate antagonist. Thus the first new medication in 47 years to treat alcoholism, naltrexone, was approved by the U.S. Food and Drug Administration in December of 1994.

Unlike Antabuse, the currently prescribed medication that causes the user to suffer severe nausea, headache, and other unpleasant effects when he or she drinks alcohol, naltrexone works by reducing the craving for alcohol and the reinforcing effects of alcohol, thereby increasing abstinence and reducing rate of severe relapse. When combined with other interventions, in one study naltrexone allowed as many as three-quarters of alcoholics to avoid a severe relapse, compared with fewer than half of those who received counseling alone.

Currently the NIAAA is funding ten studies on naltrexone. Some of these are evaluating the effectiveness of longer-term treatment and predictors of response, comparing alternative treatment approaches--such as that typically available in a primary care setting vs a more traditional and focused addiction treatment clinic--to be used in conjunction with naltrexone, and working to determine the mechanisms of naltrexone's beneficial effect. Researchers are also attempting to identify antagonists to specific subtypes of opioid receptors affected by alcohol consumption--naltrexone interacts with two, and possibly three, such receptors--as a means of developing a more narrowly targeted medication.

In conclusion, today we are entering a new era in alcohol research. We are developing priceless new knowledge in the field of genetics that will help us to improve the effectiveness of our prevention and treatment efforts. Indeed we are moving into a world where human and animal research are merging. Neuroscience has revolutionized our approach to studying the alert brain. The first twenty five years of research are now producing results in treatment and prevention which stem from basic science. We are finally beginning to understand why for some individuals alcohol becomes the dominant and destructive force in their lives.

Mr. Chairman, the fiscal year 1996 request for NIAAA is $185,712,000. I will be pleased to answer to any questions that you have.

Enoch Gordis, M.D.
Director
National Institute on Alcohol Abuse and Alcoholism

Enoch Gordis, M.D., became the Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in October 1986. Prior to this, he was Professor of Clinical Medicine at Mt. Sinai School of Medicine, New York City, and a staff member of the Elmhurst Hospital in Elmhurst, N.Y., where he founded and directed the hospital's alcoholism program from 1971 until his appointment to NIAAA. This large comprehensive program, with both inpatient and outpatient components, served some 15,000 patients during his tenure.

The NIAAA, a part of the U.S. Department of Health and Human Services' (HHS) National Institutes of Health (NIH), is the principal Federal agency for research on the causes, consequences, treatment, and prevention, of alcohol-related problems. Through an intramural scientific program, which includes a 14-bed clinical research facility on the National Institutes of Health (NIH) Bethesda, Maryland Campus, and through an extensive array of extramural research grants and contracts, NIAAA supports studies in a variety of biological and behavioral areas such as, neurosciences, pharmacology, epidemiology, genetics, molecular biology, and prevention and treatment. The Institute also supports research training and health professions development programs, and research on alcohol-related public policies that provide HHS and other Federal, State, and local government decisionmakers with state-of the-art analyses of the relationships between public policies and alcohol-related problems. The current NIAAA budget is $190.1 million.

Dr. Gordis trained in internal medicine at the Mount Sinai Hospital in New York. During this period, he also was a research fellow in Dr. Solomon Berson's laboratory at the Bronx Veterans Administration hospital. Following his residency, Dr. Gordis spent 10 years at New York City's Rockefeller University in the laboratory of Dr. Vincent Dole, conducting research in the areas of lipid metabolism, toxicology of carbon tetrachloride, analytical biochemistry of drug stereoisomers, the metabolism of alcohol and alcohol withdrawal. He has published on the clinical evaluation of alcoholism treatment, biological markers of drinking, disulfiram therapy, and the relationship between science and social policy.

As NIAAA Director, Dr. Gordis' principal goal is to continue support for activities designed to give maximum visibility to the Institute's role as a leader in alcohol-related research and the integral part of that role in preventing and treating alcohol abuse and alcoholism. This will include continued support for NIAAA's extramural and intramural research programs; support for a continuing Institute role in health professional education; increased attention to public policy research; and enhanced data collection and dissemination activities.

A member of Phi Beta Kappa, Dr. Gordis received his B.A. degree from Columbia University in 1950 and M.D. degree from the Columbia College of Physicians and Surgeons in 1954. He is a member of the Institute of Medicine of the National Academy of Sciences, the American Physiological Society, the American Federation for Clinical Research, Sigma Xi, the American Gastroenterological Association, the American Society of Addiction Medicine, the Research Society on Alcoholism, and Fellow of the American College of Physicians.

PROGRESS IN ALCOHOL RESEARCH

Mr. PORTER. Dr. Gordis, I realize that your function primarily is research. But you opened with some statistics to show how much of a burden the problem of abuse of alcohol and alcoholism is on our society. And I come from the town where Francis Willard put together the seven million signatures that led to amending the Constitution to ban alcohol, obviously a solution that was not the answer to the problem.

The Institute that you head has been in existence for at least 25 years. I wonder if you could tell us, are we really making any progress on this problem? Are we better off now than we were 25 years ago, or are people still, because this is perhaps in some sense voluntary, perhaps not better off? How much progress are we making on saving ourselves from ourselves?

Dr. GORDIS. That's a long question, Mr. Porter. But I'll try not to be too long in answering it. There has been a general change in attitude and public approaches to alcohol, which I think stems partly, but not entirely, from science, as well as specific scientific advances which I think are promising new treatments and prevention methods.

It's clear that research has had a role in legitimizing the public concern with alcohol issues, not as a matter of morality, but rather as a medical problem which can be addressed with all the tools of medical research, both behavioral and biological. At the same time, there's no question that consciousness raising has occurred in the country as a result of people outside the research community, such as Alcoholics Anonymous itself, and the various groups against drunk driving. There has been an educational and perceptional change about the role of alcohol in this country over the last 25 years, in which research has operated but cannot be given sole credit.

We are making very important progress in alcohol. Issues of driving, prevention, concern about the teenage use of alcohol, deaths on the highway, binge drinking in college, have all come to the public fore and public attention in ways which reflect the intersecting progress of medical research, the media, and the public awareness.

As far as the specific contributions of research, we can point to several consequences of research, both in the biological and in the behavioral spheres, which are quite tangible. For example, the death rate among young people on the highways went down subsequent to the Congressional action essentially mandating the illegal use of alcohol below the age of 21.

As you know, when that legislation was passed it was protested by one of the States, and the Supreme Court upheld the legislation. One of the strongest reasons the Supreme Court, we believe, did so, was on the basis of the research that the NIAAA had supported at the time; this indicated that given the fact that young people on the highways are disproportionately represented in highway deaths, this kind of legislation was likely to save the lives of our youngsters, and indeed it did. In fact subsequent research revealed that even when those affected by this legislation reach the age of 21, that subsequent drinking habits are less intense than they would have been had that legislation not been passed.

The development of Naltrexone is the fruit of both clinical observation and neuroscience. Had it not been for a long history of the study of opiate antagonists and consummatory behavior in general, and on alcohol in particular, it would not have been possible to move this field along as rapidly. Now, the clinical application of Naltrexone came initially from observations in patients but linked with extensive basic research, it meant that a medication could be approved very rapidly. This was based also on the two major studies that the NIAAA supported on the efficacy of Naltrexone in a tightly controlled research protocol. This represents one tangible example of basic science, together with good clinical observation, leading to a promising new therapy which in the pharmacological field, is the first one in 47 years.

Furthermore, in terms of public awareness— and I'll make this the last point, because I know there are other issues to be discussed—NIAAA can be said to be almost solely responsible for developing the entire scientific portfolio on the fetal alcohol syndrome, and the effects of alcohol on fetal development in matters more widely distributed but less severe than the total fetal alcohol syndrome. Certainly, the public has become highly aware of this. Our research on this question has led to one of the two contents of the warning labels on beverage alcohol. And clearly, the public consciousness of this issue is immense now. I think we can say there's been significant progress.

Mr. PORTER. Well, let me try to quantify it, or ask you to quantify it. Can you put it in terms of per capita consumption of alcoholic beverages, the number of alcoholics, the cost to society as a percentage of our gross national product? Is there progress being made that we can point to and say, yes, we've turned this thing around and it's now headed downhill, or are we still going uphill, or are we level? I guess that's what I'd like to know.

Dr. GORDIS. Yes. It's a mixed answer, Mr. Porter. Per capita consumption, except for the last couple of years when it has been rather stable, has been going down since the early 1980s when it arrived at its peak. There is certainly less tolerance of drinking and driving, and more awareness of the fetal alcohol effects.

On the other hand, it's still a very major problem. One way of carving up the cost issue from the point of view of an individual American citizen is to essentially divide that cost out and indeed it costs each person $800 to $1,000 a year. Part of the cost which is of great interest these days when we're considering economic issues so extensively is the fact that about $13 billion out of the $98 billion estimate is due to the treatment of alcoholism itself, a minor piece of it, and the treatment of its complications, a major piece. But the rest of it stems from losses of productivity, of income and matters which severely affect our economic posture.

The widespread dissemination of messages about the misuse of alcohol on all sides of society has had a tremendous impact on this country as well. That is why even modest improvements in both treatment and prevention, short of a total cure, will have an immense influence on our national well-being and economy.

Mr. PORTER. Thank you.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Gordis, nice to see you again.

Dr. GORDIS. Same here, Mr. Stokes.

Mr. STOKES. Thank you.

ALCOHOL RELATED BIRTH DEFECTS

Dr. Gordis, to what extent are birth defects attributed to the use of alcohol?

Dr. GORDIS. Alcohol is the leading cause of preventable mental retardation. The NIAAA has been the leader and probably the sole major participant in the research on this, since the first cases were described in France in 1968, and the first American paper came out of Seattle and subsequently Boston in the early 1970s. Over the last 20 years or so, a large volume of research on many aspects of this has been developed.

It is clear now that the fetal alcohol effects have to be viewed essentially as two kinds. One is the classic syndrome, with major physical malformations, with which I think you are familiar. Perhaps more important is the fact that for every one of those children, there are many, many others, who do not display the complete syndrome and perhaps no visible physical malformations at all, but in whom there are subtle yet important developmental defects, in intellect, in perceptual skills and so on, which persist for many years.

If you would like, I can elaborate a bit further. There are difficulties in estimating the prevalence of the full syndrome, mostly because it is difficult to identify at birth. And those data bases which depend on identification at birth produce one set of figures, while those that depend on following children at least through the age of one year render a higher number.

Our best current estimate is that between 4,000 and 12,000 kids are born annually with the full syndrome, but many, many more have developmental defects which are not quite so florid, but which affect their lives in a very conspicuous fashion.

ALCOHOL RESEARCH IN GENETICS

Mr. STOKES. Doctor, let me ask you whether we are seeing any major payoffs in the application of gene therapy to the treatment of alcohol abuse and alcoholism.

Dr. GORDIS. We are not yet in the position to perform gene therapy in alcoholism. However, if I may take a minute or two to share with you some of the work that we're hoping to lead to major genetic insights with applications for treatment, I will do so. May I, Mr. Stokes, proceed with this a bit?

Mr. PORTER. Certainly.

Dr. GORDIS. Thank you.

It has been known for probably about 20 years now, or maybe 15, as a result both of classical adoption studies as well as twin studies, that there is a component of the vulnerability to becoming alcoholic which is inherited. I said that carefully, because alcoholism is not a solely genetic issue. There are many profound environmental effects on the development of alcoholism. And even among those who have a genetic effect, it clearly varies among different sets of people.

As a result of these findings, it is clear that we have to engage in a serious search for those genes which account for that portion of the vulnerability which is inherited. And for that purpose, we have a major genetic study now in progress, in its sixth year, which is doing exactly that. It is moving from these population genetic studies to the studies of highly informative families in which all the tools of current molecular biology and linkage analysis are being applied to discover which genes go through these families and accompany the development of alcoholism.

Parallel to this is the fact that our field has been one of the leaders in the application of animal genetics to the study of alcoholism. This permits us to study animals which have been bred to demonstrate certain specific effects—whether it's preference for alcohol, sensitivity to the temperature lowering effects of alcohol, the development of withdrawal symptoms, or development of tolerance.

NIAAA researchers use species of animals that can be bred exactly for this research. New approaches called quantitative trait loci are applicable to diseases like alcoholism in which a single gene does not account for the disease, rather a whole group of genes does. This animal research will offer clues to make our search for the human genome even more efficient.

The genetics cooperative study is now in its sixth year. Over 5,000 people have been interviewed extensively. We hope that by the time the project is over and available for the public use of this material in two years, we will have several hundred very informative families and several thousand samples in our repositories for the study of DNA.

The final thing I'd like to mention is the reason we do this work. Because I think that's obviously behind your question. We do this work for three reasons. First of all, by developing our knowledge of the genes that lead to alcoholism, we will understand more about the physiology of alcoholism, and be able to develop more effective medical therapies. The second outcome of successful genetic research will be to be able to be more focused in our prevention efforts. And the third outcome, as we have learned many times in medicine, is that from the disease we learn much about the normal state. We will learn a great deal about the function of the human brain in terms of motivation and consumption and reward systems, which will apply far beyond the borders of the alcoholism mission to many other branches of neuroscience.

Mr. STOKES. Thank you, Dr. Gordis.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Ms. Pelosi.

ALCOHOL AND DISABILITY

Ms. PELOSI. Thank you, Mr. Chairman. My apologies for not being here for the National Institute of Nursing Research. But we have welfare reform legislation coming to the floor today. In fact, what we were debating just now is whether committees should be meeting while we have such an important issue on the floor. We'll probably have a vote on that shortly. Certainly both venues are very important, and it's unfortunate to have this conflict.

In any event, I was interested to hear what Dr. Gordis had to say in response to my colleague's question about the genetic research that you are doing. And I'm particularly interested today, because we do have the welfare reform bill on the floor. As you may know, Dr. Gordis, that bill provides that individuals are not considered disabled if alcoholism is a contributing factor material to their disability, thereby dropping them from SSI. If they're dropped from SSI, of course, they lose their Medicaid eligibility and the access to treatment that program may provide.

In light of what you have said about the vulnerability that is genetic, and what you said also about the role of the environment in alcoholism, would you contend that alcoholism in many cases has involuntary aspects to it, that it is an illness and that it should be material to someone's eligibility for SSI, so that the individual can have access to the treatment?

Dr. GORDIS. Let me preface my answer to your question with a statement that as a research institute, our task is to provide the best science-based information to the people who support us, that is, the American public. And to be clear about what we do know, to be equally forthright about what we don't know and what we're uncertain of, and basically not to replace the functions of advocacy organizations. Because if we begin to do that, I think we lose our credibility as a science agency.

DISABILITIES FROM ALCOHOL

Ms. PELOSI. I agree.

Dr. GORDIS. However, I had a different life before I came here, and part of my life was directing a treatment program for alcoholism in the State of New York, where I had the privilege to be responsible for the care of over 15,000 people in a period over a decade. Also, I am familiar with the realities of the world, such as the issues of SSI and welfare.

And the fact is that in the contemporary treatment of alcoholism there are certain things which have to be accomplished to be sure that the patient understands that he or she has a role in his or her own recovery. Even diseases which have clear genetic effects do not necessarily alleviate the patient of some share in their own recovery.

Allow me to provide an editorial view on the SSI issue, not based on the portfolio of our Institute, but more on my previous experience as the director of a treatment program, if you'll permit this. This is not my main role here, however I'll be glad to comment.

When is alcoholism a disability, or one that should be essentially paid for by SSI? There are certain aspects of alcoholism, even in the sober state, which lead to disabilities, some of which are reversible, and some of which are not. I refer to individuals who are recovering now, and who are sober. For example, cerebellar disease, which is a product of alcohol misuse which leads to permanent ataxia, that is staggering gait and so on and so forth, is a permanent effect of alcohol, even in someone who is absolutely sober and doing very well. There are pertinent aspects of dementia. Alcoholism is one of the leading causes of dementia in this country, second to Alzheimer's which was discussed during the last testimony.

Chronic liver disease, certain fractures which may have resulted from injuries which are disabling, and so on also pertain.

In my view, these are perfectly legitimate disabilities for support. What has catalyzed the response to this issue is the fact that there have been abuses and that some people have received public support for the disability during the time when they were drinking without adequate monitoring to be sure they were entering treatment and improving their lives.

Unfortunately, this is a perfect example, in my view, and I know there are disagreements on this, of throwing out the baby with the bath water. There are abuses which should have been corrected, but there are also legitimate disabilities from alcoholism which are persistent, even in the sober state, which should have been supported.

I want to say, however, that I'm speaking on this as an editorialist, based on long clinical experience and not necessarily representing the scientific views of the NIAAA.

Ms. PELOSI. I appreciate that very much. But could I conclude from what you have said that alcoholism, in the cases that you have mentioned, is a contributing factor material to disability?

Dr. GORDIS. Yes, it certainly was. The right management of disability payments and the timing of it is a matter which depends on treatment skills and adequate monitoring.

Ms. PELOSI. I fully agree with what you are saying. Thank you.

Should I wait for the next round, Mr. Chairman? Thank you.

From your work at the NIAAA or in your previous life——

[Laughter.]

NALTREXONE

Ms. PELOSI. I want to commend you for your research and all the work that you have done. And I wondered if you could tell us about the effectiveness of Naltrexone, your new medication to treat alcoholism?

Dr. GORDIS. Our Institute supported the two main studies which led to the recent approval by the FDA of Naltrexone for the treatment of alcoholism. One of the two groups was Dr. Joseph Volpicelli in Dr. O'Brien's group in the University of Pennsylvania. The other is Dr. Stephanie O'Malley and her colleagues at Yale. They published results from tightly controlled clinical trials with a placebo design, with randomization, and they found essentially in both cases two principal outcomes. Both studies were conducted over a period of three months following detoxification from alcohol.

I should point out that alcoholism treatment involves essentially two steps: the safe escort of the patient through the withdrawal, which is relatively straightforward, although there are some issues there, too. The main problem is the maintenance of sobriety, or the long-term management of alcoholism. And Naltrexone deals with that.

In the three-month studies researchers found that the time to the first drink in the case of people who did relapse, was increased. That is, the abstinence was longer in both groups who received Naltrexone. And second among individuals who slipped, that is, began to drink, the rate of progressing to a full blown binge was also dramatically different between the treatment of the placebo groups.

Another feature which must be emphasized is that Naltrexone alone was not the entire therapy; in both cases it was combined with various verbal therapies. Whether Naltrexone would be sufficient in itself without these, we do not know from research, but would highly doubt.

As a result of this, Dupont Merck received permission from FDA to market Naltrexone, which is a drug which has been long ago approved for the treatment of heroin addiction, where it has, I would say, indifferent results except in a small subset of perhaps very highly motivated patients. FDA approved this existing drug for use in the treatment of alcoholism, given the fact that the research results are from tightly controlled clinical trials in two studies and for a period of three months.

Naltrexone appears to be safe. The doses used did not produce any serious toxicity at all. On occasion, there was some nausea, and that was about all. We are now following up this research with nine or ten other approved grants, most of them on Naltrexone, one of them on a similar drug called Nalmefene, which may have less tendency to produce nausea. These studies will be for longer periods of time, and many of them are coupled with studies in the neurosciences to understand further the mechanism by which Naltrexone achieves its effect.

MODERATE CONSUMPTION

Ms. PELOSI. I appreciate that. I wish you much luck obviously with that research and that solution, hopefully. So many people are depending on the success of your work.

I heard, being from California and being a Mediterranean myself, I was interested in your recent speech before the American Heart Association writers forum, where you acknowledge that there appears to be a protective effect from moderate alcohol consumption. I say Mediterranean because I read that as wine. Considering that heart disease is the leading cause of death in this country, what kinds of research projects should be conducted in order to clarify moderate alcohol consumption's protective role, if any, in preventing heart disease. Also could you define moderate consumption.

Dr. GORDIS. I don't want to be long-winded, so I'll try to abbreviate this discussion. The Institute was created in order to solve the problems that alcohol produces; that certainly is our main mission. We do the best we can in presenting science to the public. At times we have to give guidance to the people about what their drinking decisions ought to be and we refer not to alcoholism now, but to alcohol use. It is important to know what the complete set of tradeoffs is from both the benefits and the risks.

The issue that you refer to is a complex one. The evidence is now overwhelming that when we use coronary artery deaths, for example, as an end point, that moderate drinking is protective. And although there was some question about this, the epidemiological data is quite overwhelming on this topic.

However, there are certain ambiguities and contradictions which must still be resolved. The first one is, that it is not clear that the effect is beverage specific at all, despite the fact that there are certain branches of the beverage industry who have more of an interest in this than others.

The second question is that, once one moves away from moderate drinking, one moves into a whole set of increased risks for many other effects like hypertension, some negative cardiac effects, liver disease and so on. A number of these are problematical at levels which begin slightly above the moderate drinking level.

Furthermore, there are certain groups of people who should not drink alcohol at all. Women who are pregnant or attempting to conceive should not be drinking at all; individuals who have a history of alcohol problems in the family should be thinking seriously about whether they should be drinking or not; I'm not saying I should prescribe it, and those who are recovering alcoholics should not be drinking.

The mechanisms by which alcohol exerts this protective effect are matters of great interest. They include the effects on plasma lipoproteins, which is a long-term issue; effects on platelet aggregation, which has to do with the immediate blood clot that leads to a heart attack, which is a short-term issue; and issues of the so-called antioxidants which are present in red wine but are not present in white wine and other beverages.

However, there are serious issues here which have to be resolved, such as whether antioxidants are absorbed at all in wine, because what you show in the test tube in the laboratory does not necessarily correspond to what is absorbed in the beverage which is consumed. The public health issues which surround this are of course considerable, too.

MODERATE DRINKING

But I think for the sake of time I won't go into it now, except to make one distinction, which I think is important. The role of the physician giving advice to an individual about what his or her drinking decisions ought to be is a separate job from what a public health recommendation should be for the entire public. These actually have two separate goals.

This question is a very complex one. Moderate consumption generally means for men, two standard drinks a day, for women one, and for older people probably one also, because of their somewhat increased sensitivity to its effects.

RESEARCH ON MODERATE DRINKING

Ms. PELOSI. If I may, Dr. Gordis, part of the question was also what research, what kinds of research projects should be conducted. Is there anything in the works?

Dr. GORDIS. Yes, we will solicit applications from the field on this topic. We are interested in basically two kinds of data: the mechanisms by which this protective effect could be manifested, and this complex issue of antioxidants.

The issue of the tradeoffs is a key one. Each period of life is different in terms of tradeoffs. A young person is not in danger of dying of a coronary. This young person is in danger of dying of a highway crash or homicide. A very old person may have passed the major risk for certain other diseases, but then moderate drinking perhaps brings new dangers, the danger of a drug interaction or the danger of a fall, and once one has a fracture, the quality of one's life is altered permanently. Thus, middle aged people probably have the most to gain from the judicious use of alcohol for this purpose.

Some of the mechanisms by which moderate drinking may cause this protection involve starting to drink in the teens. For example, the platelet aggregation and the immediate clot effect will happen immediately after drinking. But the changes in plasma lipoprotein, for example, have to do with the chronic development of atheroma over a period of many years. The question is, do we want to encourage people at a young age to drink for a benefit which might happen from that mechanism 20 years down the road? Thus, the issues of the changing risk and benefits of alcohol through the life span are another topic which we hope research will address.

Ms. PELOSI. Thank you very much, Dr. Gordis.

Thank you, Mr. Chairman.

BREAST CANCER AND ALCOHOL

Mr. PORTER. Dr. Gordis, just a few additional questions. Your budget identifies a modest increase in funding associated with breast cancer research initiatives. What activities are you conducting in this area and what do we know about the breast cancer-alcohol link?

Dr. GORDIS. The breast cancer-alcohol link at best is a modest one. And even within those limits, it is probably still controversial. The National Cancer Institute and others have reviewed this literature on several occasions in a very scholarly way over the past years. Most of the evidence seems to show that if there is a link between alcohol and breast cancer, the relative risk is on the order of perhaps 1.2 or 1.3, a modest increase in risk from even moderate drinking.

The mechanism which is proposed for this, granting that it's true and not all but most of the data fit this, is probably that alcohol in general has an estrogenizing effect. This means alcohol tends to increase the activity of the system of female sex hormones, which may relate to the increased propensity for breast cancer. That is probably the most I can say of the relationship at the present time. It is a modest one, and the relation of alcohol to other cancers is much more extensive and far better established.

ALCOHOL, ESTROGEN, AND OSTEOPOROSIS

We are especially interested in the alcohol estrogen relationship, however, Mr. Porter, because the whole issue of osteoporosis, especially in post-menopausal women, has come to the fore. That is another area where moderate drinking may have some protective effect. On the other hand, we know that more severe levels of drinking interfere with bone density, partly because of the noxious effects on vitamin D metabolism, a complex issue of dose, which we are very anxious to continue to study.

LIVER DISEASE

Mr. PORTER. In your testimony last year, you stated that cirrhosis is the ninth leading cause of death. I know you're trying to prevent cirrhosis through the reduction of alcoholism. But is your Institute also involved in research in finding ways to prevent alcohol from doing damage to the liver, even if it is consumed?

Dr. GORDIS. Yes, we are. Toxicology, or the effect of alcohol on various organs is of course a major part of our portfolio, including the liver diseases you refer to, and including the possible reversal of early memory defects even in anamnestic disorders of the brain.

Liver disease is an issue which has matured over the last 15 years. Originally, perhaps 20 or 25 years ago, there was some question of whether alcohol itself was a liver toxin, or whether liver disease did not simply result from malnutrition, which was so common among those who were drinking heavily.

We now know as a result of pioneering experiments that Dr. Lieber and his colleagues in the Bronx in New York conducted in primates that alcohol itself, even in the presence of a nutritious diet, is a liver toxin. The mechanism by which this occurs has engaged researchers over many, many years. In recent years, we have been very much interested in the various inflammatory factors called cytokines, which lead to inflammation of the liver and the various aspects of collagen metabolism, collagen being the protein which forms normal connective tissue as well as scars. We know now that alcohol leads to this.

We have a clinical trial ongoing with polyunsaturated lecithin as an effort to abort the progress of alcoholic liver disease to the final and most serious aspect of it, which is cirrhosis, essentially a destructive diseases of the liver characterized by widespread scarring.

This compound may increase the activity of collagenase, an enzyme that chews up scar tissue. It is too early to be confident absolutely that it will work, or that this is the pertinent mechanism. However, it is a critical topic, and we are very encouraged by the initial work.

Mr. PORTER. Dr. Gordis, we could, I'm sure, spend an entire morning at least talking with you about these very important issues. Unfortunately, we have three Institutes to cover this morning. And so all we can do is thank you for your very good testimony and your very candid answers to our questions. We covered a lot of territory that maybe was a little bit outside of the research responsibilities, and we very much appreciate your very good answers to those questions. And thank you for your testimony.

25 YEAR ANNIVERSARY FOR INSTITUTE

Mr. STOKES. Mr. Chairman, before we close, I'd like to just make an observation. I believe this is the year in which this Institute will celebrate its 25th anniversary, am I correct?

Dr. GORDIS. That's right, Mr. Stokes. It is. And we are very pleased about the activities that are planned in relation to that. We will have an all day symposium on May 3rd at NIH. And during the year, various national organizations in various disciplines, both behavioral and biologic, have been kind enough to host special sessions on alcohol issues, either symposia or plenary sessions. It is an exciting year for us, and for good science.

Mr. STOKES. We certainly want to commend you and your Institute for the outstanding work you do.

Dr. GORDIS. Thank you very much.

Mr. PORTER. I don't know, Lou, how long you've been here, but I've been here for three-fifths of the Institute's lifetime, at least. You do outstanding work, Dr. Gordis, we very much appreciate it.

Dr. GORDIS. Thank you.

[The following questions were submitted to be answered for the record:]

FETAL ALCOHOL SYNDROME

Mr. Porter: What progress has been made in understanding the danger of alcohol to the fetus?

Dr. Gordis: Progress in our understanding has been attained in several areas. Following the first clinical reports that alcohol was implicated in a specific pattern of abnormalities, it was suggested that the underlying cause might be complications from malnutrition, hypoglycemia, liver disease, or other conditions associated with the alcoholism of the mother. Animal studies have demonstrated unequivocally that alcohol is a teratogen capable of inducing a variety of birth defects. Moreover, alcohol can affect the development of sperm, and animal studies have shown that paternal alcohol consumption can affect offspring development and behavior.

We know that there are critical periods during pregnancy for different kinds of damage. For example, facial abnormalities are associated with alcohol exposure during the first trimester, whereas damage to the developing brain can occur throughout pregnancy. Ethanol affects many aspects of neuronal development, including cell proliferation, migration, synaptogenesis, and myelination, as well as neurotransmitter function. Depending on the timing of exposure, neurological damage may be manifested as cognitive, motor, or behavioral deficits, reflecting regionally specific injury to the brain. Advances in our knowledge of normal development and the availability of molecular biology techniques make it possible to explore the cellular and molecular mechanisms underlying fetal injury to the brain. Several plausible hypotheses are being explored with the hope of developing pharmacological or behavioral therapies.

Through animal research binge drinking was shown to be potentially more deleterious than steady drinking of the same quantity of alcohol, because higher blood alcohol levels are achieved with binge drinking. Human epidemiological research has demonstrated that alcohol-induced injury less severe than the full FAS can occur when drinking occurs at more moderate levels. These usually take the form of more subtle behavioral and cognitive problems without the physical signs of FAS. Studies which have followed groups of FAS children and those exposed to moderate alcohol show that children do not outgrow many of their problems as they mature.

NIAAA was responsible for establishing the fact that FAS is indeed caused by alcohol per se and activating efforts to alert women and the medical community to the dangers of drinking during pregnancy. This led to a host of prevention-related activities, including the 1981 Surgeon General's advisory, and the Alcoholic Beverage Labelling law of 1988.

Mr. Porter: Do you have any plans to conduct a research demonstration or clinical trial on the reduction of FAS? How much would such an effort cost?

Dr. Gordis: The Fetal Alcohol Research Center is a multidisciplinary resource for fetal alcohol research supported by NIAAA. One of the research components in the NIAAA Fetal Alcohol Research Center is developing and testing a model for reducing FAS. The focus is on intervention with high risk women during the second pregnancy. Later this year we hope to initiate an epidemiological study of a high risk population. This sets the stage for expansion into a preventive intervention with a clinical trial and such an effort would use the tools we have developed through research. The study to be initiated will cost approximately $1 million over four years.

RESEARCH DISSEMINATION

Mr. Porter: Please describe your efforts to disseminate your research findings to practitioners and the public.

Dr. Gordis: NIAAA disseminates scientific information to scientists, clinicians, practitioners, and the health care system. For example:

NIAAA's Triennial report of **Alcohol and Health**, mandated by Congress, is under preparation.

Alcohol Health & Research World: The **Alcohol Health & Research World**, a peer-reviewed journal, disseminates recent research findings to a diverse audience ranging from physicians to students. Published quarterly, each issue typically focuses on a single thematic topic. Recent themes have included FAS, Genetics, and Women's Health.

Alcohol Alert: The **Alcohol Alert** serves as a rapid response bulletin to communicate important research findings to clinicians and allied health professionals on specific topics. Published quarterly, the bulletin is available free of charge from the Institute and the National Clearinghouse on Alcohol and Drug Information. The **Alcohol Alert** mailing list contains over 20,000 names. The bulletin is also sent to approximately 15,000 treatment centers.

Alcohol and Alcohol Problems Science Database (ETOH): The Alcohol and Alcohol Problems Science Database, more commonly known as the ETOH Database, is the most comprehensive online bank of information on alcohol-related research. Available through BRS Information Technologies, a commercial vendor, the database contains over 80,000 records. ETOH covers all aspects of alcohol-related research beginning in the late 1960's to the present. Each month, between 200 and 300 new records are added to the database.

Scientific Exhibits and Conferences: NIAAA displays and staffs the NIAAA scientific exhibit at professional conferences around the country. Institute publications and grant announcements are displayed and distributed at the conferences. In addition, the exhibit also demonstrates the Institute's databases, promotes awareness of NIAAA programs, and encourages new research applications by identifying and facilitating contact with program staff.

The NIAAA and the National Foundation for Brain Research sponsored a meeting, "The Neuroscience of Alcoholism: Advancing Hope in the Decade of the Brain."

In connection with the NIAAA 25th anniversary recognition, 17 outside organizations such as the American College of Neuropsychopharmacology, the American Society of Human Genetics, the Society for Neuroscience, the Society for the Study of Ingestive Behaviors and the Research Society on Alcoholism, have invited the Institute to give symposia.

FETAL ALCOHOL SYNDROME AND ETHNICITY

Mr. Porter: What do we know about the risk of FAS in whites versus various minority groups?

Dr. Gordis: Despite general population declines in drinking during pregnancy, Fetal Alcohol Syndrome remains the leading preventable cause of mental impairment. Among known alcoholics, African Americans, and some Native American groups, the incidence appears to be significantly higher than among the majority healthy white population. It is possible that the higher incidence of Fetal Alcohol Syndrome observed in some ethnic populations may mean that those populations are, indeed at increased risk for alcohol teratogenesis. For African Americans, the risk of Fetal Alcohol Syndrome remains about sevenfold higher than for whites, even after adjustment for frequency of maternal alcohol intake, parity, and occurrence of chronic alcohol problems. Among Native Americans, the incidence of Fetal Alcohol Syndrome varies among different cultures. Factors such as patterns of alcohol consumption, cultural differences, nutrition, and metabolic differences may play roles in these differences. An important strategy for preventing alcohol-related birth defects is the development of better screening techniques to identify women at high risk for heavy alcohol consumption throughout their pregnancy. NIAAA-supported investigators have developed a simple and brief questionnaire to help circumvent denial and underreporting of heavy drinking by pregnant women.

DISTINCT GENETIC UNDERPINNINGS OF ALCOHOLISM

Mr. Porter: Dr. Gordis, your Institute is making a substantial investment in the genetic underpinnings of alcoholism. Do you think it is likely that the genetics findings for alcoholism--for example, genes that may identify susceptibility--may also have applicability for drug abuse, or are these likely to be genetically distinct phenomena?

Dr. Gordis: Alcohol research is in an advantageous position with respect to genetics, since our studies have been underway for approximately twenty years; genetic research related to drug abuse is a newer topic. In general, we do not yet know the answer to your question. It may be found that some portion of a genetic basis for alcoholism vulnerability is shared with that for drug abuse, while some is not. It is also possible that some metabolic property of alcohol is key. The evidence from family studies is inconsistent and it will take time to resolve this matter. Thus it is too early to offer a definitive answer to your question.

Mr. Porter: We understand that naltrexone has been approved by FDA as a treatment for alcoholism. It seems as if we have been hearing about naltrexone and its promise for a number of years. Has the FDA approval process slowed the availability of a drug that has been identified for some time?

Dr. Gordis: Naltrexone was for some time identified as a treatment for heroine addiction. More recently it was identified as a tool in treating alcoholism, and has undergone appropriate testing. The FDA approval process was accomplished in a timely manner.

Mr. Porter: How comprehensive a solution is naltrexone likely to be for the alcohol-dependent population? Must it be used in conjunction with behavioral therapies?

Dr. Gordis: Researchers and clinicians alike are optimistic about the usefulness of naltrexone as an adjunct to conventional alcoholism treatment. It is the first medication in forty-seven years to be approved for that purpose. The studies which led to that approval utilized a combination of naltrexone and verbal therapies. We do not have data at this time about its effectiveness if used without verbal therapies, but would be skeptical if this would be productive.

MEDICATIONS DEVELOPMENT

Mr. Porter: What other treatment drugs are in the pipeline from your medications development initiative?

Dr. Gordis: NIAAA currently has twelve medications under investigation. Ten of the medications Institute scientists are studying work to reduce drinking. These include the opioid antagonists naltrexone and nalmefene, serotonin re-uptake inhibitors fluoxetine and sertraline, tricyclic antidepressants imipramine, desipramine, and nortriptyline, dopamine agonist bromocriptine, the anxiolytic agent buspirone, and lithium. To treat acute alcohol withdrawal, Flumazenil, a benzodiazepine antagonist, is being tested. To prevent alcohol-induced liver fibrosis a pilot trial is being conducted on alcoholics using phosphatidylcholine, a polyunsaturated soybean lecithin.

TREATMENT FOR ALCOHOLISM

Mr. Porter: Dr. Gordis, can you review for us how well currently available treatments work? What are the long-range abstinence rates for the various approaches?

Dr. Gordis: It is difficult to summarize such a complex issue. Different measures of improvement exist, but if long term abstinence is the goal, then in general conventional treatment gives long term abstinence in about one third of cases, the others will not appear for review or will relapse and require further treatment. Because alcoholism is a chronic relapsing disease, we can meaningfully measure how much time the patient becomes improved. In treatment of arthritis, for example, we might say that the patient was pain-free nine months out of twelve. As a result of the kinds of progress we are making in treatment, for example with naltrexone and patient-treatment matching, we are very optimistic about improving the health of alcoholic patients.

FETAL ALCOHOL SYNDROME: PREVENTION AND RESEARCH

Mr. Porter: There is continuing interest in the fetal alcohol syndrome (FAS). Do you think the major effort at this point should be in prevention or research?

Dr. Gordis: As a research institute, NIAAA seeks to develop the underpinnings for successful prevention efforts. Prevention and research efforts are not mutually exclusive--in fact they complement each other. Prevention efforts at any level are not likely to be effective unless there is a sufficient knowledge base derived from research to suggest appropriate approaches.

Alcoholism prevention research designs and tests interventions to prevent alcohol-related problems, develops methods and instruments for measuring intervention outcomes, and examines social processes that facilitate or hinder the effective implementation of prevention strategies. The goal of NIAAA-sponsored prevention research is to obtain scientifically objective and measurable effects attributable to specific interventions. To ensure the acquisition of meaningful results that are generalizable to other locations, these studies employ rigorously defined scientific methodologies,including random selection and control communities. Good examples of our research are NIAAA's community intervention studies. These trials are based on the proven effectiveness of two other NIH-sponsored community-based trials: the completed cardiac risk reduction study and the extant smoking cessation study, COMMIT. Community-based trials are long-term, controlled experiments testing multifaceted, integrated prevention programs at the community level.

Mr. Porter: What new efforts do you have underway at your Institute with regard to FAS?

Dr. Gordis: The NIAAA has the lead for the new IOM study on FAS which has an emphasis on prevention. A report is expected in August of 1995.

of 1995.

The Institute sponsored an international conference at Wayne State University on the Fetal Alcohol Syndrome in the fall of 1994. Topics included the extent of the FAS problem, social/community intervention, clinical intervention, and strategies for individuals.

NIAAA hopes to initiate a new epidemiological study later this year in a specific high risk population. This will set the stage for expansion into preventive intervention.

PATIENT-TREATMENT MATCHING

Mr. Porter: You have been conducting a large-scale patient treatment matching trial. Where does that effort stand?

Dr. Gordis: Project MATCH is the largest most complex randomized clinical trial ever undertaken in alcoholism treatment. A total of 1728 patients were recruited with ample representation of women (25%) and minorities (20%) have been enrolled in nine sites. Three specific treatment approaches were tested: Twelve Step Facilitation; Cognitive-Behavioral Coping Skills Therapy; and Motivational Enhancement. These three approaches were precisely detailed by participating investigators and NIAAA staff in handbooks which were published and generated considerable interest by nonparticipating practitioners.

The project consists of two independent treatment-matching studies, one with clients recruited at five outpatient settings, the second with patients receiving aftercare treatment at four sites following an episode of standard inpatient treatment. Patients were randomly assigned to one of the three treatment approaches. Each study evaluates the interaction effects between selected patient characteristics and the three treatments.Quality control of verbal therapies was assured by videotaping and observation by blinded analyzers. The Coordinating Center concluded a major inter- and intra-site reliability study of the four most complex assessment interviews.

This approach permits simultaneous testing of various treatment strategies, exploration of interactions between strategies and standardization of techniques among participating centers. Beyond yielding a priori hypotheses, the rich data base generated will allow exploratory analyses on other effective ways to assign patients to alcoholism treatment.

Project MATCH has completed patient intake, intervention and follow-up of all patient and has now entered an intensive data analysis phase. Rates of attendance at therapy and for research follow-up sessions were exceptional, especially in comparison to the usual rates obtained in studies of substance abusing populations. Overall about 75% of all scheduled therapy sessions were completed. Attendance at follow-up sessions to obtain research data for the first year after treatment was likewise high, averaging around 90% Results of the studies of the accuracy and reliability of the data collection and quality of the therapy administration were excellent, indicating that the study was carried out according to protocol and therefore the resulting data will have high validity.

Analysis of the extensive data base is now the focus of the study. Preliminary reports are expected next fall. Numerous other publications on the methodology of the study have been published and were well received by the scientific community. Interest in the potential of the trial for clinical practice is evident in that the first two printings of the three therapy manuals published by NIAAA have already been exhausted and a third printing is underway.

Mr. Porter: Last year, you indicated that you were considering a three-year extension of the trial. What did you ultimately decide?

Dr. Gordis: In FY 1994, this trial successfully recompeted for another three years of support. Analysis of the extensive database generated by this research will be the focus of the final three years.

COMMUNITY PREVENTION TRIALS

Mr. Porter: Your justification indicates that you are using the community prevention trial model to research youth access to alcohol and trauma reduction. Do the resource requirements of community prevention trials strain the budget of an Institute the size of yours?

Dr. Gordis: Because our research project grant budget is relatively small, the Institute must always weigh the potential adverse impact that expensive grants may have on the stability and balance of our portfolio. With regard to our community trials, this is one of the research areas where we collaborate with the Substance Abuse and Mental Health Services Administration (SAMHSA) and share most of the costs.

MODERATE ALCOHOL CONSUMPTION

Mr. Riggs: Dr. Gordis, as you know, our Committee put forth Congressional Appropriations language urging Health and Human Services to study the health effects of moderate alcohol consumption. We are very pleased to see that NIAAA is planning to issue a Request for Applications (RFA) to seek research proposals in this area. I would like to reiterate that this area of research is very important as it may benefit the American public.

What steps are you taking to develop the "working strategy" called for in the Appropriations language to assure future research on the impact of moderate alcohol consumption and health?

Dr. Gordis: In keeping with the Appropriations language, NIAAA has developed a request for applications. The Institute is requesting research applications to determine both beneficial and harmful effects associated with moderate alcohol consumption. Clearly, the NIAAA was created in order to solve problems that alcohol produces; that is our central mission. However, when asked to present science to the public in the form of guidance regarding their decisions in terms of moderate drinking, we wish to emphasize the importance of knowing the complete picture of tradeoffs, both beneficial and risky. A number of ambiguities and contradictions need to be resolved. Questions to be addressed include: Do health benefits ascribed to moderate drinking, such as decreased risk of coronary artery disease, apply equally to different segments of the population? What are the exact cellular and molecular mechanisms by which alcohol confers these benefits? Is moderate alcohol consumption associated with specific health risks? What are the public health issues surrounding this matter? Answers to such questions will help to identify the tradeoffs involved in individuals' decisions about drinking. This approach will also provide a better understanding of the mechanisms involved in alcohol's effects in general.

Mr. Riggs: Dr. Gordis, I heard about your recent speech before the American Heart Association's Writers Forum where you acknowledge that there appears to be a protective effect from moderate alcohol consumption on cardiovascular disease.

Considering that heart disease is the leading cause of death in this country, what kinds of research projects should be conducted to clarify moderate alcohol consumption's protective role in preventing heart disease? Also, could you define moderate consumption?

Dr. Gordis: First, moderate drinking means, for men, two standard drinks per day and for women, one standard drink per day. Older people should probably ingest no more than one drink per day because they have a somewhat increased sensitivity.

Research aimed at more clearly defining the circumstances that increase risk and the categories of individuals who are at risk for alcohol-related problems will help individuals and the professionals who advise them to make more informed decisions concerning alcohol use. Better understanding of the biological mechanisms involved in the cardioprotective aspects of moderate alcohol use also could lead researchers to find alternate ways to provide the same protection.

Mr. Riggs: Dr. Gordis, some recent research has suggested that the wine-consuming regions in Mediterranean countries not only have lower rates of chronic diseases but also lower rates of alcohol abuse. Also, most of the U.S. population who drink do so without developing alcohol abuse problems.

Would it be worthwhile to investigate such non-problematic drinking patterns in that it might help further the understanding of how to prevent alcohol abuse? What kind of research could you plan in this areas? Should it involve the development of appropriate public education approaches?

Dr. Gordis: NIAAA has developed a Request for Applications concerning the issue of moderate drinking which has received so much attention of late. Institute researchers continue to investigate the effects of public education approaches. They are particularly interested in designing effective community preventive intervention studies. In addition to examining the role of moderate consumption in various illnesses and the interaction of alcohol with medications, the request for applications addresses benefits versus harm of drinking. Could the decrease in coronary artery death due to moderate drinking be offset by alcohol-related injuries? Because motor vehicle accidents are relatively common at younger ages, should years of life gained from a decrease in coronary artery disease not be compared to years of life lost due to accidents? Would encouraging abstainers to drink moderately alter the alcohol consumption curve, leading to more alcohol abuse? What are the benefits versus risk for different groups of people, such as the elderly, women, the young, smokers, etc.? These and other questions which require investigation are posed in the Institute's Request for Applications.

ALCOHOLISM TREATMENT: MEDICATIONS DEVELOPMENT

Mr. Stokes: The Institute recently reported a new treatment for alcoholism, naltrexone. According to the Institute's media advisory, this medication is considered to be safe and effective. What can you tell us about this new treatment and the hope it offers the more than 1 million Americans treated for alcoholism each year? What are the side effects of the treatment and to what extent does it also create a dependency for the patient? What is the possibility of this treatment causing birth defects?

Dr. Gordis: NIAAA has been investigating pharmacologic agents as promising adjunctive agents for the treatment of alcoholism. Four types of pharmacologic agents have been used for treating alcohol dependence: agents that alleviate withdrawal; agents that reduce the desire to drink alcohol; **agents that decrease drinking by treating associated psychiatric pathology**; and **agents that directly suppress problem drinking.** Research on pharmacologic treatment of alcoholism has dramatically expanded at NIAAA in recent years. Special advances have been made in developing medications that decrease the desire to drink. One of the most promising medications appears to be the orally active opioid antagonist, naltrexone. Naltrexone was approved for treatment of alcoholism by the Food and Drug Administration in 1994.

Two recent clinical studies of **naltrexone** on alcohol dependent patients have shown it to be effective in reducing the number of days drinking, attenuating the level of craving for alcohol, and decreasing the rate of relapse. Interestingly, if patients do "slip" and have one or two drinks, those on naltrexone are less likely to continue drinking than are placebo-treated subjects. One study compared psychosocial interventions in combination with naltrexone and found that the type of psychosocial intervention influenced outcome. The naltrexone/supportive therapy group achieved the highest abstinence rate, while recipients of the naltrexone/coping skills therapy experienced the lowest rate of heavy drinking. Currently, ten studies are being funded by NIAAA on naltrexone to address several important clinical issues. These include investigating the long-term efficacy of naltrexone, defining long-term risks and side-effects, identifying subtypes of alcoholics who may respond most favorably to naltrexone, integrating naltrexone treatment with psychosocial therapies, and exploring new opioid agents. The Dupont-Merck research showed the safety of naltrexone to be very good. There were basically no adverse side effects besides, on occasion, dizziness and nausea. Patients who have liver disease should not take this medication. There is no evidence that naltrexone causes birth defects but this has not been proven. It has been in use for a number of years in the treatment of heroine addiction, so it has a well demonstrated safety record. Patients will not develop dependency because the medication works as a blocker. Researchers are hopeful because this is the first medication to reduce desire to drink. There is promise in further research along these lines. Naltrexone seems to be an important tool for treating alcoholism.

TREATMENT MATCHING AND GENETICS COOPERATIVE AGREEMENT

Mr. Stokes: According to the congressional justification, the Institute's Project MATCH clinical trial is the largest most complex randomized clinical trial ever undertaken in alcoholism treatment. What progress can you report to the committee at this time from Project MATCH and also from the Genetics of Alcoholism Project?

Dr. Gordis: Project MATCH is the largest most complex randomized clinical trial ever undertaken in alcoholism treatment. A total of 1728 patients were recruited with ample representation of women (25%) and minorities (20%) have been enrolled in nine sites. Three specific treatment approaches were tested: Twelve Step Facilitation; Cognitive-Behavioral Coping Skills Therapy; and Motivational Enhancement. These three approaches were precisely detailed by participating investigators and NIAAA staff in handbooks which were published and generated considerable interest by nonparticipating practitioners.

The project consists of two independent treatment-matching studies, one with clients recruited at five outpatient settings, the second with patients receiving aftercare treatment at four sites following an episode of standard inpatient treatment. Patients were randomly assigned to one of the three treatment approaches. Each study evaluates the interaction effects between selected patient characteristics and the three treatments.Quality control of verbal therapies was assured by videotaping and observation by blinded analyzers. The Coordinating Center concluded a major inter- and intra-site reliability study of the four most complex assessment interviews.

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Analysis of the extensive data base is now the focus of the study. Preliminary reports are expected next fall. Numerous other publications on the methodology of the study have been published and were well received by the scientific community. Interest in the potential of the trial for clinical practice is evident in that the first two printings of the three therapy manuals published by NIAAA have already been exhausted and a third printing is underway.

COGA is a large multi-disciplinary, multi-site collaborative study involving six extramural research study centers. The COGA investigators are searching the entire human genome for genetic markers which are linked (co-transmitted with) alcoholism. In the process of this search, they will be able rigorously to test the involvement of a number of genes hypothesized to contribute to susceptibility to alcoholism, and perhaps discover contributions from other genes not yet suspected of involvement with alcoholism. Now 5400 interviews of alcoholics and their family members have been conducted; 800 pedigrees have been established and cell lines from 1848 individuals are available for genetic analysis. Biochemical, neurophysiological, and neuropsychological characterization of more than 1500 individuals provided further information to accompany the extensively detailed clinical assessment of the recruited subjects. Genotyping of 900 subjects at more than 100 genetic markers has begun. So far nearly 20,000 genotypes have been entered into the database.

Thus, two valuable resources, Cell and Data Repositories, are being established and maintained by COGA. These substantial collections of alcoholic pedigrees and associated data, together with their cell lines will become available to the research community at the end of 1999. They will serve as a critical and unique resource for future studies of the genetics of alcoholism. By that time, phenotypic and genotypic data and biological materials for at least 200 extended families or 3000 individuals will have been accumulated

Another major contribution made by COGA is the development and validation of several diagnostic instruments. The success of family and genetic linkage studies in alcoholism and other psychiatric diseases depends on valid, reliable, and specific information. To address the limitations of existing instruments, COGA investigators developed several comprehensive instruments, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) and it's companion version for children (C-SSAGA-C) and adolescents (C-SSAGA-A)These new instruments addressed a gap in currently available psychiatric instrumentation by covering a wide range of diagnostic classification systems, by paying close attention to different diagnoses, and by providing an array of items suitable for the broadest descriptions of phenotypes. The onset, co-morbidity, drinking patterns, and severity of disorder can be assessed and subtypes of alcoholics identified.

Finally, the multiple diagnostic classification systems of SSAGA allow COGA data to be compared with existing family, epidemiologic and genetic data sets. Confirmation of findings from earlier studies is thus possible.

CLINICAL TRIAL FUNDING

Mr. Stokes: How much is included in the FY 1996 budget request for each of these initiatives, and how does this compare with the current funding level?

Dr. Gordis: In the FY 1996 President's request, $2,355,000 is included for Project MATCH, the multi-site treatment clinical trial, and $6,530,000 for the Cooperative Agreement on the Genetics of Alcoholism. These funding levels reflect a 3 percent increase over the FY 1995 levels of $2,300,000 and $6,335,000, respectively.

Mr. Stokes: With respect to clinical trials in general, how many trials would be funded under the FY 1996 budget request funding level? How many of these trials are new and how many are ongoing?

Dr. Gordis: In the FY 1996 President's request, NIAAA would support 65 clinical trials; 2 would be new and 63 would be ongoing.

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously? Is there a specific system in place for disseminating such information? Explain.

Dr. Gordis: Yes, we are doing well at disseminating the results of clinical trials expeditiously. One excellent example is the dissemination of findings from our studies of naltrexone, which have been swiftly disseminated through various avenues. Another good example is the dissemination of products of Project MATCH. This has proceeded smoothly and has resulted in considerable demand. Numerous publications on the methodology of the study have been published and were well received by the scientific community. Interest in the potential of the trial for clinical practice is evident in that the first two printings of the three therapy manuals published by NIAAA have already been exhausted and a third printing is underway.

Also consensus development conferences offer an opportunity to spread information from trials efficiently.

TRENDS IN CONSUMPTION AMONG YOUTH

Mr. Stokes: What is the extent of alcohol abuse in children and adolescents? Have we seen an increase or a decrease in the past five years, and do we know why?

Dr. Gordis: Some of the figures show an increase and some show a decrease, but drinking among youth and young adults remains a concern. In general, the NIDA senior survey found that youths' perception of risk involved with drinking increased in recent years. Some improvements may be attributed to prevention efforts, and some to social changes. The relationship between public policies and the level of alcohol consumption requires further scientific investigation.

- Based on the 1993 National Household Survey on Drug Abuse, the percentage of current alcohol users for 12-17 year-olds was 18.0 percent, up from 15.7 percent in 1992. Current alcohol use slightly rose among 18-25 year-olds 59.3 percent in 1993, compared to 59.2 percent in 1992. In 1993, 41.3 percent of 12-17 year-olds and 87.1 percent of 18-25 year-olds reported drinking at sometime in their lives.

- 1994 data from the annual NIDA survey of high school seniors show that:

- Although reported use of alcohol continued to gradually decline in the 1980's and early 1990's, there has been slight increases in 1993 and 1994;

- 80.4 percent of 1994 seniors reported drinking at sometime in their lives, up .4 percent from the previous year's seniors;

- 2.9 percent drank every day, fewer that the 1979 high of 7 percent, but still representing daily use by 1 in 40 seniors;

- Episodes of heavy drinking (i.e., 5 or more drinks at a time) during the two weeks preceding the survey were reported by 28.2 percent in 1994, up .7 percent from 1993.

- 73.0 percent reported alcohol use during the past year, compared to 72.7 percent in 199350.1 percent reported use during the past month, compared to 48.6 percent in 1993.

RESEARCH OPPORTUNITIES

Mr. Stokes: Please describe the most promising opportunities in basic as well as clinical research you anticipate for the next several years, and elaborate on the benefits that could be derived from investment in these areas.

Dr. Gordis: We believe the following areas are most promising and will have the highest payoff.

1. The Mechanisms of Uncontrolled Alcohol Intake.

The most crucial issue in alcohol research today is why some people drink uncontrollably. Uncontrolled alcohol intake results from a complex interaction among genetic, biological, and environmental factors. Several neurotransmitters have been identified as possible candidates for mediators of alcohol reinforcement; the two most important of which are dopamine and serotonin. Research on the molecular mechanisms of the reinforcing effects of alcohol on the brain, motivated drinking, and satiety is integral to understanding uncontrolled appetitive behavior, such as uncontrolled consumption of alcohol and eating disorders. Recent evidence suggests a link between eating disorders and alcoholism. Bulimic patients show an addiction-like behavior (craving, loss of control, adverse social and medical consequences) and often tend to abuse alcohol or other drugs. Animal and human studies on how the presence of alcohol alters appetitive behaviors after acute and chronic exposure, and how these behaviors are augmented or diminished by environmental cues and stress are also quite important. The resulting knowledge will broaden the scope of therapeutic interventions that can be used to reduce the reinforcing effect or craving for alcohol which will aid in the treatment of alcoholism, including the incidence of relapse.

2. Quantitative Trait Loci (QTL) Mapping

Alcoholism is a complex disease with various genetic and environmental factors which influence the development and ultimate expression of the disorder. Genetic mapping of quantitative trait loci (QTLs) contributing to alcoholism and alcohol responses is a relatively new and exciting research area. This technique gives the investigator the ability to define the contribution of a single gene to complex behaviors that are determined by the interaction of many genes and for which environmental factors are important. QTL mapping employs genetic crossing of inbred rat or mouse strains and achieves statistical power by using a sufficient number of animals. Because of the conservation of gene order during mammalian evolution, many syntenic regions between these species have been identified. Many genetic markers are becoming available that can be screened for their contribution to the expression of the complex behaviors associated with alcoholism. Once linkage is established, candidate genes in animals and humans can be identified by comparative mapping. Thus, dissection of complex polygenic traits in an animal model is leading to a rapid and effective way of identifying important genes contributing to various responses to alcohol and the susceptibility to alcoholism in humans.

3. Genetics of Susceptibility to Alcohol-Induced Organ Damage

Only a relatively small proportion of alcoholics become affected by medical complications of alcoholism (*e.g.*, liver cirrhosis, pancreatitis, cardiomyopathy, Wernicke-Korsakoff's Syndrome), and different individuals succumb to different complications. Large individual differences also occur in the incidence and severity of fetal alcohol syndrome (FAS) in the children of mothers who drink during pregnancy. Characterization and isolation of genes underlying susceptibility to alcohol-induced organ damage will allow early identification of individuals at risk. The genetic information will help improve the design of studies of environmental factors conducive to these disorders. It may ultimately improve pharmacotherapy for these disorders by facilitating the design of drugs which interact with the products of these genes.

4. Markers for Identifying Individuals at High Risk for Alcoholism

A major aim of the basic research program is to develop methods to measure an individual's vulnerability to developing alcoholism and related medical sequelae. It is important for these measures, or markers, to have high predictive value. Studies of male children of alcoholics have suggested that measures of sensitivity to alcohol challenge or of certain electrical changes in the brain can predict subsequent alcoholism among these children. Increased levels of a specific protein, Gsα, in erythrocyte and lymphocyte membranes found in nonalcoholic men who were born into families with alcoholic member(s) may be another such marker. Research along this line will allow for the early identification of and early intervention with individuals at high-risk for developing alcoholism. The fruits of NIAAA's COGA will also lead to new markers.

5. Alcohol, Estrogen and Women's Health

Alcohol is known to increase estrogen levels and alter the ratio of estrogen to other hormones. Estrogen and its receptors are known to be involved in the regulation of many cellular processes. Basic research to explore a possible causal relationship between alcohol consumption and altered hormone status in the etiology of alcohol-related medical complications such as liver disease among women is needed. Understanding how alcohol interacts with the endocrine system at the cellular and molecular level will aid in our understanding of how pathogenesis is accelerated in women. This may lead to the development of specific hormonal therapies to prevent alcohol-related pathology in women.

6. Moderate Drinking. NIAAA plans to issue an RFA and learn more about the benefits of moderate drinking.

7. The continuation of medications development and clinical trials holds significant promise for improving the treatment of alcoholism. The recent approval of naltrexone was an encouraging example of the possible fruits of this type of research. Ultimately the payoff should be enormous in terms of cost savings as well as improvement in quality of life.

8. The benefits from our patient treatment matching research and subsequent treatment research promise to allow us to invest our treatment resources more wisely which will result in more efficacious treatment for many patients and allow us to reap considerable benefits.

SUCCESS RATES AND AVERAGE COST TRENDS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years, explain.

Dr. Gordis: NIAAA has witnessed a substantial growth in the number of research project grant applications in the past ten years. The number of applications increased from 346 in FY 1986 to 453 applications in FY 1991, over a 5 percent increase annually. Since FY 1991, however, NIAAA's number of applications have grown from 453 to 719 in FY 1995, almost 10 percent on a annual basis. In the FY 1996 President's request, the number of applications is projected to be 728.

Success rates for NIAAA averaged about 31 percent for FYs 1986 to 1991 with the high being 38 percent in FY 1989 and the low being 23 percent in FY 1991. Since FY 1991, the NIAAA success rate has averaged 24 percent with the high being 32 percent in FY 1992 and the low being 19 percent in FY 1993. In the FY 1996 President's request, our success rate is projected to be about 18 percent.

Decreases in the success rates in the past five years are mainly related to the increased scientific interest in NIAAA's research program, and to a lesser extent, a leveling of budgetary increases.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same period? What is the trend in constant dollars?

Dr. Gordis: The average costs of research project grants, in total, was $122,000 in FY 1986 and has grown to $233,000 in FY 1996.

The annual increase in average costs for the ten year period is about 6.5 percent.

In terms of constant dollars, using the FY 1986 as the base year and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average cost has grown from $122,000 in FY 1986 to $149,000 in FY 1996. The annual increase in average costs for the ten year period is about 2 percent.

Mr. Stokes: What is the success rate for research applications received from minority researchers? from women? from African Americans? from HBCUs?

Dr. Gordis: To comply with federal mandates all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NIH is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women.

Using the last fiscal year for which there is data, the following identifies minority and women researchers who chose to answer the optional questions on the grant application related to gender and race, and may not provide a true representation of NIH's support of such researchers.

The following table lists FY 1994 success rates for self-identified minority researchers, including African Americans, women, HBCUs, and two categories identified as -- unknown and missing -- for those grant applicants who chose not to identify their ethnic origin and gender, respectively. The unknown category accounted for 23 percent of the FY 1994 awards.

Competing RPG Success Rates

FY 1994

Category	Rate
Asian	19.1%
African American	0.0%
Hispanic	45.5%
Native American	0.0%
Unknown Race	30.4%
White	30.2%
Female	31.5%
Male	27.3%
Missing Gender	56.3%
HBCU	0.0%
Total, NIAAA	29.2%

Mr.Stokes: For the same time period, in real and in constant dollars, what have been the average costs of research project grants awarded to women? to minority researchers? to African-American researchers? to HBCUs?

Dr.Gordis: Using the last 10 fiscal years for which there are data, the following table identifies the average cost of competing awards to women, minority researchers, including African Americans, and HBCUs. Constant dollar calculations use FY 1985 as the base and the Biomedical Research Price Deflator Index. As stated previously, questions related to race and gender are optional on NIH grant applications. As a result, the following table identifies a gender category as "unknown" which represents the average cost of competing grants for applications in which race could not be determined.

Since there is no method of estimating the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of such researchers:

Competing Grant Average Costs
in Five Year Increments FY 1985, FY 1989, and FY 1994
NIAAA
(Dollars in thousands)

	1985		1989		1994	
Category	Current	Constant	Current	Constant	Current	Constant
Asian	$89.1	$89.1	$137.5	$113.4	$114.5	$76.1
African American	74.7	74.7	125.8	103.8	---	---
Hispanic	62.2	62.2	88.6	73.1	204.0	135.6
Native American	---	---	---	---	---	---
Unknown Race	76.4	76.4	107.5	88.7	195.5	130.0
White	107.2	107.2	163.7	135.1	203.3	135.2
Female	125.2	125.2	142.5	117.6	232.9	154.9
Male	97.8	97.8	163.5	134.9	189.8	126.2
Missing Gender	77.1	77.1	117.3	96.8	102.6	68.2
HBCU	49.6	49.6	---	---	---	---
Total, NIAAA	101.9	101.9	158.1	130.4	196.7	130.8

ALCOHOLISM AND BIRTH DEFECTS

Ms. Lowey: Last year we discussed the similarities and differences between female and male alcoholics. For pregnant women, clearly prevention is a crucial element of any strategy for containing the effects of alcoholism.

You mention in your testimony NIAAA's work on prevention and effective intervention for alcohol-related birth defects, such as Fetal Alcohol Syndrome. Could you discuss this work in greater detail? Have we learned more about the scientific basis of alcoholism that could help us in our work to educate pregnant women about the dangers of alcohol?

Dr. Gordis: It is clear that education efforts that have occurred over the last two decades have had an impact on increasing knowledge that alcohol is a teratogen, and likely have had an impact on the drinking behavior of many pregnant women. Clearly though, many women still drink in a risk-provoking manner in pregnancy, and research can inform us of what can be done to effect this behavior. Health education activities, such as media education campaigns, the Surgeon General's Advisory, and warning signs, and the bottle label have helped to increase knowledge on Fetal Alcohol Syndrome and Alcohol Related Birth Defects. Ninety-two percent of women know that alcohol can be harmful in pregnancy. However, their understanding of the risk is limited --only 30% appear to understand that FAS is a life-long birth defect, not a child born intoxicated. With respect to behavior, drinking during pregnancy has decreased among women in the low risk categories, but not in the high risk.

An important research finding is that significant improvements in infant outcome can occur when women stop drinking, even in mid-pregnancy. This is especially true for the most serious manifestations of FAS and FAE, the brain function deficits in behavior and intellectual performance. Therefore, reaching pregnant women who drink is well worth the effort in and of itself. There is the added benefit as well of changing drinking behavior for the next pregnancy.

Our research has developed several excellent screening tools to identify risk drinkers in primary and obstetric care, such as the T-ACE and the TWEAK. As good as these instruments are, further efforts to develop better tools, including potential biological markers, may yield even more effective approaches. As well, screening instruments for at-risk drinking are of no use if they are not incorporated into clinical practice. Clinics and physicians' offices are busy enterprises, and screening for alcohol problems does not appear to be uniformly undertaken. Research can demonstrate both the ease and importance of incorporating such procedures.

WOMEN'S HEALTH

Ms. Lowey: We discussed last year NIAAA's plans for expanding its research on alcohol's role in elevating risk factors for diseases in women, such as heart disease, breast cancer, and stroke. You mention in this on-going work in the budget justification. You also mention that upcoming research will look into the role of alcohol in domestic violence.

Could you describe the Institute's work in this area? Have you already begun looking into alcoholism and domestic violence?

Dr. Gordis: The role of alcohol consumption in both breast cancer and osteoporosis is included in the NIH Women's Health Study, the largest clinical study of women's health ever undertaken in the history of the NIH. NIAAA has an ongoing breast cancer study using an animal model. Thus far the findings strongly indicate a linkage between ethanol and breast cancer. The results identify a cellular mechanism for ethanol-induced carcinogenesis in the rat mammary gland: ethanol may increase the number and rate of cell proliferation of the terminal end bud structures which are known targets of chemical carcinogens and in which tumors have been produced.

Researchers are also investigating the relationship between alcohol and osteoporosis. Alcohol can interfere with calcium and bone metabolism in several ways. Acute alcohol consumption can lead to a transient PTH deficiency and increased urinary calcium excretion, resulting in loss of calcium from the body. Chronic heavy drinking can disturb vitamin D metabolism, resulting in inadequate absorption of dietary calcium. Studies in alcoholics also have shown that alcohol is directly toxic to bone-forming cells and inhibits their activity. Calcium deficiency can lead to bone diseases, such as osteoporosis. Studies with abstinent alcoholics have found that alcohol-induced changes in bone metabolism, including toxic effects on bone-forming cells, are at least partially reversible after cessation of drinking.

NIAAA has a multidisciplinary research program on alcohol and violence that includes studies focused on partner violence. These studies employ cross sectional, longitudinal, and experimental designs and draw on samples that include both large cross-sections of communities and special populations. Partner violence is being studied through both extramural grants and an important Intramural research project. The Institute also published NIAAA Research Monograph No. 24, Alcohol and Interpersonal Violence which includes papers on partner violence.

PREVENTION AND TREATMENT

Ms. Lowey: Dr. Gordis, what are you doing to study how to more effectively prevent and treat alcohol abuse and alcoholism? This disease is much more costly socially and economically than is generally realized.

Dr. Gordis: Our prevention research contributes to the mission of the Institute by furnishing the basic scientific understanding, for example, to explain addiction and its mechanisms, which will consequently lead us to appropriate strategies for prevention. It will also help us learn how best to intervene with individuals who suffer from alcoholism and alcohol-related problems. In addition, it will provide the rationale for prevention strategies affecting the external environment, such as legislation and policy regarding presentation of the agent, drinking and driving, availability, and price.

The Institute is supporting community prevention trials which were designed to capitalize on the knowledge base built by community-based research projects in the heart disease and cancer prevention fields. These trials are aimed at reducing youth access to alcohol and alcohol-related trauma, for example. NIAAA is also supporting research which examines the relative contribution of biological factors to the etiology of alcohol abuse and alcoholism and their inter-relationship with family, social, psychological, and environmental factors. Research is underway to determine the family, socio-cultural, legal, and other environmental triggers that can interact with individual vulnerability and result in alcohol abuse and alcoholism.

Elements of treatment for alcohol dependence include management of alcohol withdrawal, long-term management of alcohol dependence, and prevention of relapse. Various alternative treatments are available for alcohol problems, ranging from brief, motivational interventions to "broad spectrum" treatments, such as social skills training, and Minnesota model (12-step, e.g. Alcoholics Anonymous) therapies. Some treatment regimens employ adjunctive pharmacotherapy. There are inpatient, outpatient, and self-help programs. Frequently two or more treatment modalities are combined in one therapeutic approach.

Examples of particularly promising types of treatment we are studying are pharmacotherapy and patient-treatment matching. The recent approval by the Food and Drug Administration of naltrexone as a treatment for alcoholism presages a new era in medications development. This was the first medication approved for the treatment of alcoholism in forty-seven years. We are optimistic and are conducting a number of additional studies in this area. Project MATCH is a major clinical trial we are conducting, matching patients to treatments. Components of this are brief motivational therapy and coping skills and relapse prevention. We are also studying community reinforcement which is a multifaceted approach.

ECONOMIC TOLL OF ALCOHOL MISUSE

Ms. Lowey: Dr. Gordis, what is the economic cost of alcohol abuse and alcoholism in this country?

Dr. Gordis: Alcohol abuse and alcoholism exact tolls of approximately$98.6 billion each year--yet only a fraction, $10.5 billion, is devoted directly to treatment for alcoholism, alcohol abuse and subsequent medical consequences. The remainder can be attributed to lost productivity, excess illness, and early death. Alcohol claimed more than 108,000 lives in 1989--double the number lost to AIDS--while years of potential life lost to alcohol-related diseases exceeded years lost to heart disease and approached the years lost to cancer. Our health care system registers the repercussions: 20 to 40 percent of patients in urban hospital beds suffer from the effects of drinking regardless of the conditions which initiated their hospitalizations.

PREVENTION

Ms. Lowey: Dr. Gordis, has NIAAA's research been able to determine if there are any prevention programs that work?

Dr. Gordis: NIAAA was responsible not only for establishing the fact that fetal alcohol syndrome is indeed caused by alcohol per se, but also for energizing efforts to alert women and the medical community to the dangers of drinking during pregnancy. This led to a host of prevention-related activities, including the Surgeon General's advisory and alcohol beverage labelling law of 1988. There has been a subsequent general decline in alcohol consumption during pregnancy.

NIAAA also was responsible for providing the research basis for the minimum drinking age law, dramatically reducing alcohol-related driving deaths, especially among persons 16 to 20 years of age.

There have also been positive results from an intervention based on a social skills/peer pressure resistance approach. Students were encouraged to examine the influences in their lives that promoted drinking, such as peer pressure, advertising, and social norms, and to learn ways to resist. Expectancies were examined and challenged with factual information. Students at greatest risk for future alcohol problems were most affected by the intervention. For these students, the increase in alcohol misuse over time among those receiving intervention was approximately one third of the increase among those who did not receive intervention. This research shows that school-based prevention programs beginning in the sixth grade can reduce subsequent alcohol use and misuse by high-risk youth.

MODERATION AND BREAST CANCER

Ms. Lowey: Dr. Gordis, would more moderate use of alcohol be protective against breast cancer or more harmful?

Dr. Gordis: Although most evidence suggests an increased risk for certain cancers only among the heaviest drinkers, moderate drinking may be related to female breast cancer. In one study, breast cancer was approximately 50 percent more likely to develop in women who consumed three to nine drinks per week than in women who drank fewer than three drinks per week. This indicates consumption at a level even lower than the one drink per day which is often considered moderate for women. The effect of alcohol also appears to be dose dependent, i.e., alcohol poses greater risk as doses increase.

WOMEN'S HEALTH ISSUES

Ms. Lowey: Dr. Gordis, what are some of the important research issues on alcohol and women which are currently being pursued?

Dr. Gordis: It is crucial to expand family, adoption, and twin studies of women in the search for global measures of women's risk for developing alcoholism, insight into the mechanisms underlying the transmission of alcoholism through generations, and genetic markers that signal increased risk for alcoholism in women. Studies of risk factors for alcoholism are important for identifying individuals who may be susceptible to developing alcohol abuse and alcoholism and in developing effective prevention strategies and treatment plans. In the past, many of the conclusions derived from alcohol research have either been based on male populations or have not specifically analyzed gender differences. More recent studies suggest that men and women respond differently to some physiological, behavioral, and subjective indicators of potential alcohol abuse problems. Continued research will be needed to determine the potential usefulness of these markers in the female population.

NIAAA emphasizes studies that aim to determine why women alcoholics are at increased risk for certain alcohol-related pathologies, such as liver disease. Further studies are needed to understand the mechanisms for alcohol's role in breast cancer, heart disease, reproductive disorders, hemorrhagic stroke, osteoporosis, and alcoholic liver disease. NIAAA researchers continue to investigate these topics. Of special interest is whether moderate drinking involves different or greater risks for women.

The Institute will strengthen research focused on improving treatment outcome in women by matching individuals with interventions based on patients' needs and characteristics. Examining the impact of gender differences in treatment is key. Project MATCH addresses the role of gender in the primary matching hypotheses being tested as well as other analyses.

Primary prevention for women of childbearing age and pregnant women is important. A crucial step in preventing alcohol-induced birth defects is identifying women whose drinking places them at increased risk for having children with FAS or FAE. Currently, women with high-risk drinking patterns often are not recognized in clinical settings. Research to develop improved screening approaches will facilitate the identification of these women in primary care settings, in family practice units, and in obstetric and gynecological practices. Researchers are also working to develop brief interventions that can modify high-risk drinking.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Alcohol Abuse and Alcoholism

FY 1996 Budget — Page No.

Organization chart.......... 72

Appropriation language.......... 73

Amounts available for obligation.......... 75

Budget mechanism table.......... 76

Summary of changes.......... 78

Budget authority by object.......... 80

Administrative costs.......... 82

Authorizing legislation.......... 83

Appropriation history.......... 84

Budget authority by activity.......... 85

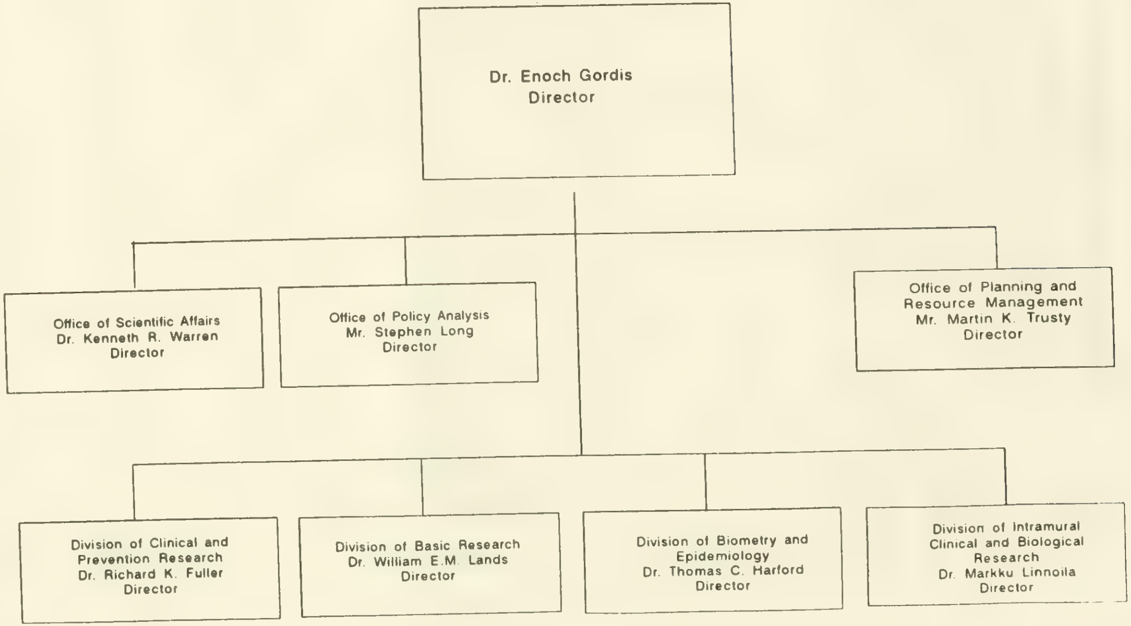
Justification:

A. General statement.......... 87
B. Extramural research.......... 90
C. Intramural research.......... 95
D. Research management and support.......... 97
E. Detail of full-time equivalent employment (FTE).......... 99
F. Detail of end-of-year employment.......... 100

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Organization Structure


Dr. Enoch Gordis
Director
Office of Scientific Affairs
Dr. Kenneth R. Warren
Director
Office of Policy Analysis
Mr. Stephen Long
Director
Office of Planning and Resource Management
Mr. Martin K. Trusty
Director
Division of Clinical and Prevention Research
Dr. Richard K. Fuller
Director
Division of Basic Research
Dr. William E.M. Lands
Director
Division of Biometry and Epidemiology
Dr. Thomas C. Harford
Director
Division of Intramural Clinical and Biological Research
Dr. Markku Linnoila
Director

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

For carrying out section 301 and title IV of the Public Health Service Act with respect to alcohol abuse, and alcoholism, [$181,445,000] *$185,712,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$185,617,000	$181,445,000	$185,712,000
Section 205 Procurement reduction.	---	-117,000	---
Section 207 Rent reduction........	---	-4,000	---
Section 216 S & E Reduction.......	---	-68,000	---
Subtotal, adjusted appropriation	185,617,000	181,256,000	185,712,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities........	-9,457,000		
Comparative transfer to: Other NIH Institutes for Management Fund adjustment....	-831,000	-844,000	
Comparative transfer to: NIH/OD for accounting charges...	-86,000	-86,000	
Subtotal, adjusted budget authority......................	175,243,000	180,326,000	185,712,000
Unobligated balance, lapsing......	-78,000	---	---
Total obligations.............	175,165,000	180,326,000	185,712,000

1/ Excludes the following amounts for reimburseable activities carried out under this account: FY 1994 - $4,194,000; FY 1995 - $4,501,000; FY 1996 - $4,525,000.

Also excludes funding for HIV activities: FY 1995 -- $9,741,000; FY 1996 -- $10,135,000, included in Office of AIDS Research, NIH.

Note: Excludes $4,370 in FY 1994 for royalties and $4,500 in FY 1995.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects						
Noncompeting	285	$68,256,000	309	$71,190,000	314	$76,374,000
Administrative supplementals	(17)	358,000	(19)	855,000	(19)	889,000
Competing:						
Renewal	47	10,044,000	40	8,919,000	38	8,816,000
New	97	18,420,000	96	18,883,000	82	16,809,000
Supplemental	3	494,000	1	205,000	1	213,000
Subtotal, competing	147	28,958,000	137	28,007,000	121	25,838,000
SBIR/STTR	8	1,394,000	12	2,319,000	12	2,414,000
Subtotal, research projects	440	98,966,000	458	102,371,000	447	105,515,000
Research Ctrs:						
Specialized/comprehensive	13	17,220,000	13	18,473,000	13	19,230,000
Other Research:						
Research career program	46	3,876,000	47	4,044,000	47	4,161,000
Cooperative clinical research	12	8,540,000	12	8,635,000	12	8,885,000
Minority biomedical research support	--	287,000	--	312,000	--	321,000
Other research related	10	972,000	12	861,000	12	886,000
Subtotal, other research	68	13,675,000	71	13,852,000	71	14,253,000
Total, research grants	521	129,861,000	542	134,696,000	531	138,998,000

Training:						
Individual awards:						
Noncompeting	11	311,000	28	524,000	12	329,000
Competing	24	388,000	13	231,000	29	448,000
Subtotal, individual	35	699,000	41	755,000	41	777,000
Institutional awards:						
Noncompeting	134	3,576,000	110	3,279,000	136	4,098,000
Competing	23	677,000	33	1,090,000	15	398,000
Subtotal, institutional	157	4,253,000	143	4,369,000	151	4,496,000
Total, training	192	4,952,000	184	5,124,000	192	5,273,000
Research and development contracts	30	8,214,000	29	8,242,000	29	8,242,000
SBIR/STTR	(10)	(888,000)	(3)	(878,000)	(3)	(965,000)
	FTEs		FTEs		FTEs	
Intramural research	101	19,324,000	106	19,247,000	106	19,815,000
Research management and support	133	12,892,000	129	13,017,000	127	13,384,000
Total	234	175,243,000	235	180,326,000	233	185,712,000
Clinical trials		(20,117,000)		(20,000,000)		(20,500,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

1995 Estimated budget authority	$180,326,000
1996 Estimated budget authority	185,712,000
Net change	+5,386,000

Changes:	1995 Current Estimate Base FTEs	1995 Current Estimate Base Budget Authority	Change from Base FTEs	Change from Base Budget Authority
A. Built-in:				
1. Intramural Research				
a. Within grade increases		$7,317,000		+$93,000
b. One day more pay		7,317,000		+29,000
c. Annualization of January, 1995 locality pay raise		7,317,000		+30,000
d. January, 1996 pay increases		7,317,000		+121,000
e. Unemployment compensation, Federal employees compensation fund increase		7,317,000		+1,000
f. Payment for centrally furnished services		5,567,000		+169,000
g. Service and Supply Fund increase		1,103,000		+46,000
h. Federal telecommunications system decrease		315,000		-4,000
i. Increased cost of supplies materials, and other expenses		4,945,000		+186,000
Subtotal				+671,000
2. Research Management and Support				
a. Within grade increases		8,915,000		+136,000
b. One day more pay		8,915,000		+34,000
c. Annualization of January, 1995 locality pay raise		8,915,000		+36,000
d. January, 1996 pay increases		8,915,000		+147,000
e. Unemployment compensation, Federal employees compensation fund increase		8,915,000		+1,000
f. Payment for centrally furnished services		352,000		+32,000
g. Service and Supply Fund increase		1,107,000		+29,000
h. Decreased cost of DHHS Working Capital Fund		169,000		-5,000
i. Federal telecommunications system decrease		265,000		-14,000

Summary of Changes-continued

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
j. Increased cost of supplies materials, and other expenses......................		$2,209,000		+$155,000
Subtotal...............				+551,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a: Noncompeting..................	309	$72,045,000	+5	+$5,218,000
b: Competing.....................	137	28,007,000	-16	-2,169,000
c: SBIR/STTR.....................	12	2,319,000	---	+95,000
Total..................	458	102,371,000	-11	+3,144,000
2. Research Centers....................	13	18,473,000	---	+757,000
3. Other research......................	71	13,852,000	---	+401,000
4. Research training awards...........	184	5,124,000	---	+149,000
5. Research and Development Contracts..	29	8,242,000	18	---
	FTEs		FTEs	
6. Intramural Research................	106	$19,247,000	---	-103,000
7. Research Management and Support.....	129	13,017,000	-2	-184,000
Subtotal...............				+4,164,000
Total changes..........				+5,386,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	235	233	-2
Full-time equivalent of overtime and holiday hours	1	1	---
Average ES salary	$112,357	$113,481	+$1,078
Average GM/GS grade	10.8	10.8	---
Average GM/GS salary	$48,084	$48,564	+$457
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	50,511	51,269	+493
Average salary of ungraded positions	21,731	22,057	+206
Personnel compensation:			
Full-time permanent	$9,801,000	$9,968,000	$167,000
Other than full-time permanent	1,832,000	1,844,000	12,000
Other personnel compensation	480,000	479,000	-1,000
Special personnel services	1,145,000	1,000,000	-145,000
Total personnel compensation	13,258,000	13,291,000	+33,000
Personnel benefits	2,892,000	2,937,000	+45,000
Benefits for former personnel	130,000	60,000	-70,000
Travel and transportation of persons	329,000	329,000	---
Transportation of things	74,000	74,000	---

	1995 Appropriation	1996 Estimate	Increase or Decrease
Rental payments to GSA	$1,477,000	$1,500,000	+$23,000
Rent, communications and utilities	840,000	997,000	+157,000
Printing and reproduction	295,000	294,000	-1,000
Other Services:			
Consulting services	38,000	50,000	+12,000
Other Services	2,613,000	2,975,000	+362,000
Purchases from Govt. Accts	7,605,000	7,895,000	+290,000
Operation of GOCOs	---	50,000	+50,000
R&D Contracts	8,242,000	8,242,000	---
Supplies and materials	1,859,000	1,866,000	+7,000
Equipment	798,000	851,000	+53,000
Grants, subsidies and contributions	139,820,000	144,271,000	+4,451,000
Insurance Claims & Indemnities	56,000	30,000	-26,000
Total, budget authority by object	180,326,000	185,712,000	+5,386,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation			
Full-time permanent (11.1)	$9,801,000	$9,968,000	+$167,000
Other than Full-time Permanent (11.3)	1,832,000	1,844,000	+12,000
Other Personnel Compensation (11.5)	480,000	479,000	-1,000
Special Personnel Services (11.8)	1,145,000	1,000,000	-145,000
Total Personnel Compensation (11.9)	13,258,000	13,291,000	+33,000
Civilian Personnel Benefits (12.1)	2,892,000	2,937,000	+45,000
Benefits to Former Personnel (13.0)	130,000	60,000	-70,000
Travel (21.0)	329,000	329,000	---
Transportation of Things (22.0)	74,000	74,000	---
Communications, Utilities, and Miscellaneous Charges (23.3)	840,000	997,000	+157,000
Printing and Reproduction (24.0)	295,000	294,000	-1,000
Consulting Services (25.1)	38,000	50,000	+12,000
Other Services (25.2)	2,613,000	2,981,000	+368,000
Purchases from Govt. Accts. (25.3)	7,605,000	7,889,000	+284,000
Operation of GOCOs (25.4)	0	50,000	+50,000
Supplies and Materials (26.0)	1,859,000	1,866,000	+7,000
Total Obligations (99.0)	29,933,000	30,818,000	+885,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amt. Authorized	1995 Appropriation	1996 Amt. Authorized	1996 Budget Request
Research and Investigation..	Section 301	42§241	Indefinite	$175,202,000	Indefinite	$180,439,000
National Institute on Alcohol Abuse and Alcoholism...............	Section 464H	42§285n	Such Sums as Necessary		Such Sums as Necessary	
National Research Service Awards....................	Section 487	42§288	Such Sums as Necessary	5,124,000	Such Sums as Necessary	5,273,000
Total Budget Authority....				180,326,000		185,712,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/	
1993	n/a	n/a	$180,169,000	$176,619,000	2/
1994	$173,615,000	$184,700,000	184,700,000	185,617,000	4/
1995 3/	182,498,000	181,328,000	181,328,000	181,256,000	
1996 3/	185,712,000				

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIAAA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $1,430,000, $61,000, and $601,000.

3/ Excludes funds for HIV Research Activities consolidated to in the NIH Office of AIDS Research in FY 1995 and FY 1996.

4/ Excludes enacted administrative reductions of $117,000, $4,000, and $68,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Alcohol biomedical and behavioral research........	--	$133,486	--	$136,440	--	$142,990	--	$148,062	--	$152,513	--	+$4,451
Intramural research.	107	17,941	112	19,991	101	19,311	106	19,247	106	19,815	--	+568
Research management and support......	141	12,093	142	12,919	133	12,864	129	13,017	127	13,384	-2	+367
Subtotal, obligations.....	248	163,520	254	169,350	234	175,165	235	180,326	233	185,712	-2	+5,386
Unobligated balance, lapsing.........	--	267	--	273	--	78	--	---	--	---	--	---
Total budget authority......	248	163,787	254	169,623	234	175,243	235	180,326	233	185,712	-2	+5,386

Justification

National Institute on Alcohol Abuse and Alcoholism

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
234	$175,243,000	235	$180,326,000	233	$185,712,000	-2	+$5,386,000

General Statement

This document provides justification for non-AIDS activities of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled, "Office of AIDS Research (OAR)".

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the foremost Federal agency for biomedical and behavioral research for improving the prevention and treatment of alcohol abuse and alcoholism and reducing associated health, economic, and social consequences. NIAAA provides leadership in the country's effort to combat these problems, by developing new knowledge that will decrease the incidence and prevalence of alcohol abuse and alcoholism, and associated morbidity and mortality.

Vulnerability to alcoholism arises from interactions between genetic and environmental causes. The particular genes conferring vulnerability are unknown, but it is clear that multiple genetic and environmental factors are involved and individuals may be affected by different factors. Over the past ten years, twin and adoption studies and studies of selectively bred animal lines have yielded evidence for genetic transmission of vulnerability to alcoholism. Advances in molecular biology have made it feasible to search systematically for individual genes contributing to a person's vulnerability to alcoholism. NIAAA's multidisciplinary collaborative study of alcoholism genetics will provide further information about familial transmission of vulnerability and the interaction of environmental and genetic factors in the expression of alcoholism--data valuable for identifying individuals at risk and designing effective preventive interventions.

NIAAA scientists study the effects of alcohol on the anatomy, physiology, biochemistry, and molecular biology of the nervous system. Alcohol exhibits a multitude of effects on the nervous system by interfering with ionic and molecular events, cellular metabolism, cell-to-cell communication, and hormonal functioning that ultimately impair the balance between neurotransmission and behavior. The key to discovering how alcohol addiction develops rests with understanding the molecular actions of alcohol on neurotransmitter receptors, ion channels, and signal transduction systems as they relate to addiction, tolerance, and physical dependence. Scientists are exploring the contributions of neurobiological, genetic, and environmental factors leading to uncontrolled drinking. With the advent of advanced biochemical and neuroimaging technologies, neuroscience research is progressing briskly with investigators working to discover the molecular, cellular, and behavioral bases for the action of alcohol on the brain.

Today better understanding exists concerning alcohol metabolism and its role in the process of addiction and pathological consequences of alcohol abuse. Research has deepened comprehension of alcohol's impact on the central nervous system and has improved our knowledge of the neurotransmitter systems involved in intoxication and dependence. Also, understanding of alcohol-related medical disorders is improving as the Institute continues to probe the mysteries of alcohol's effects.

The President's appropriation request of $185,712,000 for this account represents current law requirements. No proposed law amounts are included.

Funding for the NIAAA during the past five years has been as follows:

	Amount	FTEs
FY 1991	$150,252,000	239
FY 1992	163,787,000	248
FY 1993	169,623,000	254
FY 1994	175,243,000	234
FY 1995	180,326,000	235

Purpose and Method of Operation

The Division of Basic Research, the Division of Clinical and Prevention Research, and the Division of Biometry and Epidemiology are extramural research entities that support a wide range of research efforts in their respective functional areas through research grants, contracts, cooperative agreements, National Research Service Award fellowships, and training grants. The Division of Biometry and Epidemiology is also involved in data collection and analysis on distribution and determinants of alcohol abuse and alcoholism through studies and surveys.

The Division of Intramural Clinical and Biological Research includes laboratories engaged in metabolic, preclinical, and clinical research.

The Institute's staff offices provide policy analyses, peer review, and business management of grant applications and contract proposals and awards, as well as personnel, planning, management analysis, administrative, financial management activities in support of Institute programs. The Office of the Director provides overall management and direction, assesses program operations and effectiveness, and establishes the Institute's goals, objectives, and priorities.

In both its intramural and extramural activities, the Institute conducts and supports research aimed at determining the causes of alcoholism, discovering how alcohol damages the organs of the body, and developing prevention and treatment strategies for application in the Nation's health care system; serves as a national resource for the collection, analysis, and dissemination of scientific findings and improved methods of prevention of alcohol-related problems and treatment services; supports training and development of scientists for participation in alcohol research programs and activities; conducts policy studies that have broad implications for alcohol prevention, treatment, and rehabilitation activities; and conducts epidemiological studies as well as national and community surveys to assess the risks for and problems among various population groups.

Overall Budget Policy

The FY 1996 request for NIAAA is $185,712,000, an increase of $5,386,000 or 3.0 percent over the FY 1995 appropriation of $180,326,000. A program increase of $83,000 is also included in the FY 1996 request for the breast cancer research initiative.

The FY 1996 request will support 447 total research project grants at $105,515,000, a decrease of 11 awards from the FY 1995 appropriation. In FY 1996, NIAAA would support 314 noncompeting research project grants at $76,374,000, compared to 309 non-competing research project grants for $71,190,000 in FY 1995; 121 competing grants at $25,838,000 compared to 137 competing research project grants for $28,007,000 in FY 1995, and 12 SBIR grants at $2,414,000. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. Average costs of competing research project grants would receive an increase equal to the Biomedical Research Price Deflator Index (BRPDI) of 4.2 percent.

A total of 13 research centers would be supported in the FY 1996 request at $19,230,000, an increase of $757,000 or 4.1 percent over the 1995 appropriation.

A 2.9 percent increase over the 1995 appropriation would be provided for other research grants. This includes 47 research careers at $4,161,000; $8,885,000 for the Cooperative Agreement on the Genetics of Alcoholism and for Project MATCH; $321,000 for Minority Biomedical Research Support; and $886,000 for 12 awards comprised of instrumentation awards, and conference and scientific evaluation grants.

The FY 1996 request would support 192 full-time training positions at $5,273,000, an increase of eight training positions over the FY 1995 appropriation and a funding increase of $149,000 or 2.9 percent.

Research and development contracts would be supported at $8,242,000, the same level as the 1995 appropriation.

The FY 1996 request includes $19,815,000 for intramural research and $13,384,000 for research management and support, an increase of 2.9% and 2.8%, respectively, over the FY 1995 appropriation. FTEs are 233 compared to 235 in FY 1995.

National Institute on Alcohol Abuse and Alcoholism

Extramural Research

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part C Sections 464H and 487.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$143,027,000	$148,062,000	$152,513,000	+$4,451,000

To fulfill its research mission, NIAAA places its greatest emphasis on extramural studies conducted by scientists in universities, colleges, and other institutions throughout the country to build a solid base of biomedical and behavioral knowledge for improved prevention and treatment of alcohol-related problems. This extramural activity supports studies in such areas as health services, genetics, Fetal Alcohol Syndrome (FAS), alcohol-related medical disorders, and medications development; studies that are designed to investigate alcohol treatment and prevention methods and strategies; and epidemiological research aimed at understanding the etiology of alcohol abuse.

Funding for this activity during the last 5 years has been as follows:

	Amount
FY 1991	$121,823,000
FY 1992	133,605,000
FY 1993	136,663,000
FY 1994	143,027,000
FY 1995	148,062,000

Rationale for the Budget Request

The FY 1996 request for extramural research, which consists of the activity, alcohol biomedical and behavioral research, is $152,513,000, an increase of $4,451,000 or 3.0 percent over the FY 1995 appropriation of $148,062,000.

The National Institute on Alcohol Abuse and Alcoholism

YOUTH

Alcohol and Birth Defects. Alcohol is a teratogen capable of inducing congenital defects, growth retardation, learning disabilities, and other behavioral disturbances. Alcohol's adverse effects on the fetus exist along a continuum, with complete Fetal Alcohol Syndrome (FAS) at one end of the spectrum and incomplete features of Fetal Alcohol Effects (FAE), including more subtle cognitive-behavioral deficits, on the other. The NIAAA was responsible for discovering FAS and galvanizing efforts to alert women and the medical community to the dangers of drinking during pregnancy. NIAAA also has the lead for the new Institute of Medicine Study on FAE and FAS.

In FY 1996 researchers will continue to develop a scientific basis for effective prevention and intervention of FAS and FAE. Especially targeted will be those women who have not been reached and women whose drinking behavior has not been changed by current efforts. Also research will explore the genetic attributes of the fetus which may contribute to susceptibility to the effects of alcohol. NIAAA scientists will conduct basic biomedical research focusing on how prenatal exposure to alcohol disrupts normal fetal development by exploring alcohol's effects on developmental gene regulation and neural cell division. Clinical studies on FAS to determine when during pregnancy the fetus is at greatest risk from alcohol exposure and the long-term effects of prenatal exposure to alcohol are crucial. Other areas of emphasis include research on the effects of youthful drinking on the adolescent brain, the roles of genetic, individual, and environmental factors, as well as longitudinal studies of children of alcoholics.

MEDICATIONS DEVELOPMENT

New Pharmacotherapy for Alcoholism. A primary goal of NIAAA's medications development program is to identify medications that block alcohol-seeking behavior. Institute researchers will continue working to develop pharmacological agents that limit craving for alcohol, block alcohol's reinforcing effects, or produce an aversive reaction when combined with alcohol. Excessive consumption of alcohol results in physical dependence; liver cirrhosis; pancreatitis; gastritis; cardiovascular disorders; certain cancers; alcohol-related dementia; and immune, endocrine, and reproductive illnesses. Therefore, another top priority is for NIAAA scientists to develop medications to palliate directly or even reverse the organ damage caused by alcohol. Two recent NIAAA clinical trials have shown particularly promising results in treating alcoholism with naltrexone, which was very effective in reducing both alcohol craving and alcohol consumption. Naltrexone is a medication that binds to the body's naturally occurring opiate receptors. Alcoholics treated with naltrexone experienced fewer days drinking, had less craving for alcohol, a smaller number of heavy drinking episodes, and less alcohol use after relapse. In fact, recent studies indicate that significantly fewer patients treated with naltrexone returned to heavy drinking compared with those treated with placebo. In the future, advances in understanding brain neurochemistry and physiology, particularly the biological bases for alcohol use and the phenomenon of craving, will provide new pharmacotherapeutic possibilities. Development of new medications to prevent relapse to alcoholic drinking will have a major positive impact on the effectiveness of treatment for alcoholism. In addition, the cost of health care should be reduced. These leads hold exciting promise for alleviating the suffering caused by alcohol abuse and alcoholism.

GENETICS

Genetic Vulnerability. NIAAA researchers will proceed with their studies of the genetic basis of alcoholism and alcohol-related pathology. Investigators continue to search the entire human genome for genetic markers which are linked (co-transmitted) with alcoholism. In the process of this search, they will be able to test rigorously the involvement of a number of genes hypothesized to contribute to susceptibility to alcoholism, and perhaps discover contributions from other genes not yet suspected of involvement with alcoholism. This major multidisciplinary, collaborative research study involves six research institutions throughout the Nation. It is a pedigree study that uses molecular genetic techniques to establish the genetic typing of individuals in families in which alcoholism is multiply represented. Such research has the potential to shed light on the seemingly increased vulnerability to alcohol-related problems of some minority group populations.

Application of Quantitative Trait Loci (QTL) Mapping in Genetic Research. Animal research has permitted the testing of hypotheses concerning the relationship of animal alcohol-related behaviors and human alcohol-related behaviors. QTL mapping is a method for teasing out the contributions of individual genes to a trait (such as vulnerability to alcoholism) which is influenced by many genes. QTL mapping provides an objective test for beginning to understand the relevance of alcohol related mouse behavior to human alcoholism. QTL methods have been designed for use in animals and rely on crosses between defined inbred strains. QTL analysis provides a speed and precision unavailable in human studies. Methodology is now being developed, however, to use QTL statistical analysis on the human genome. These methods promise to be extremely useful. The most important advantage of QTL mapping is that it permits the identification of genes whose products participate in behavioral and physiological responses to alcohol, even in the absence of prior hypotheses about what role their products might play in such responses. From these animal studies, NIAAA investigators can develop new insights which can then be applied to humans.

TREATMENT

Patient Treatment Matching. Although a number of therapies have had varying degrees of success, no single treatment has been shown to be effective for all persons with alcohol problems. In recent years, interest in the field has focused increasingly on patient-treatment matching to improve outcome. The hypothesis is that more beneficial results can be obtained if treatment is prescribed on the basis of individual patient needs and characteristics as opposed to treating all patients with the diagnosis of alcoholism in the same manner. NIAAA's Project MATCH is the largest most complex randomized clinical trial ever undertaken in alcoholism treatment. Three specific, precisely documented treatment approaches are being tested: Twelve Step Facilitation; Cognitive-Behavioral Coping Skills Therapy; and Motivational Enhancement. This approach permits simultaneous testing of various treatment strategies, exploration of interactions between strategies and standardization of techniques among participating centers. Beyond yielding a priori hypotheses, the rich data base generated will allow exploratory analyses on other effective ways to assign patients to alcoholism treatment. In FY 1996 investigators will continue analyzing data from this trial. The results of this research can yield tremendous cost savings.

NEUROSCIENCE

Brain Imaging. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are now widely used as diagnostic and research tools to assess structural and functional abnormalities in many disease states. These and other tools such as single photon emission computed tomography (SPECT), electroencephalography (EEG), event-related potentials (ERP), and magnetoencephalogram (MEG) can be used to assess the nature and extent of brain injury resulting from in utero alcohol exposure, for example. Another important research area is imaging of the brain to study appetitive motivations and behaviors. Preliminary motivational studies evoking the experience of craving by olfactory stimulation are being conducted in NIAAA's intramural laboratories with functional MRI. This year the NIAAA extramural program will continue to amass data on the neuroscience of alcohol-seeking behavior in animals.

Impulsivity and Serotonin. Impulsivity or behavioral disinhibition and high levels of risk-taking behavior are associated with people who become alcoholic early in life. Impulsivity may be associated with random, unprovoked violent behavior, and high-risk sexual behavior that can lead to infection with HIV. Frontal lobe damage in humans often leads to behavioral disinhibition and diminished cerebrospinal fluid (CSF) levels of 5-HIAA, the major metabolite of the brain neurotransmitter serotonin. NIAAA scientists found CSF levels of 5-HIAA to be reduced in a white, homogenous Finnish population with frontal lobe damage and those with a history of impulsive behavior. A variation in a gene has been discovered which associates with low CSF 5-HIAA levels and a history of suicide attempts in impulsive alcoholic offenders. As other such genes are found, genetic and behavioral studies will be carried out on non-human primates to discover the effects of these variations.

Evidence for the Interaction of Alcohol with Neurotransmitter Receptor Proteins. For almost a century it has been thought that alcohol effects in the central nervous system resulted from actions on membrane lipids. This "lipid theory" of alcohol action resulted from a correlation between the lipid solubility of short-chain alcohols and their potency for producing behavioral effects. Consequently, for many years, any effects of alcohol on membrane proteins were assumed to be secondary to the effects on membrane lipids. Recently, two NIAAA intramural studies have produced evidence that various alcohols can interact directly with neurotransmitter receptor proteins. Since a number of neurotransmitter receptors have already been cloned, the molecular sites of alcohol's action on membrane receptors will soon be elucidated. This promises powerful new approaches to medications development.

PREVENTION

Community Trials. NIAAA's community prevention trials are based on the proven effectiveness of two other NIH-sponsored community-based trials: the completed cardiac risk reduction study and the extant smoking cessation study.

Community-based trials are long-term, controlled experiments testing multifaceted, integrated prevention programs at the community level. Two of these trials are the Youth Access Trial and the Trauma Reduction Trial. The Youth Access Trial is a randomized community trial of interventions devised to reduce youth access to alcohol in 15 small Minnesota communities. The Trauma Reduction Trial is comprised of interventions designed to reduce alcohol-related trauma and is being conducted in matched pairs of communities: one pair in California and one pair in South Carolina. Other community-based trials funded by NIAAA that seek to reduce trauma, prevent adolescent drinking, and reduce drinking and driving will be continued. Future research is needed to promote the delineation of the complex interactions between youth and their social and physical environments, identify cognitive processes that mediate risk, and develop interventions appropriate to specific risk levels and developmental stages. Interventions that promote personal competency; enhance intrafamily interaction; and maximize peer, school, community, health care, and legal environments to prevent underage drinking require precise documentation and rigorous evaluation. This work will be continued under the FY 1996 President's Budget Request.

WOMEN'S HEALTH

The NIAAA's specific goals include: conducting family, adoption, and twin studies of women to gain insight into the mechanisms underlying the transmission of alcoholism through generations; and supporting basic genetic research, especially genome scanning, targeted gene disruption, and animal studies, to identify the specific genes that confer vulnerability. There is emphasis on studies that seek to determine why women alcoholics are at increased risk for certain alcohol-related pathologies, such as liver disease and to examine any association between alcohol use and breast cancer. In FY 1996, research areas of special interest include improving treatment outcome and the role of alcohol in domestic violence.

MINORITY HEALTH

Special NIAAA goals for Minority Health are to: stimulate analytical studies of the epidemiology of alcohol problems in ethnic and racial minority populations; encourage research to determine whether people of certain minorities possess unique genetic, socio-cultural, and environmental determinants that increase or decrease their risk for alcoholism and related pathologies; and encourage analytical studies to determine special treatment needs that may exist for minority communities. Targeted research in FY 1996 will address specifically the alcohol related problems of these diverse populations.

National Institute on Alcohol Abuse and Alcoholism

Intramural Research

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part C Section 464H.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
101	$19,324,000	106	$19,247,000	106	$19,815,000		+$568,000

The NIAAA Intramural Research program conducts a comprehensive research program through a full range of studies that not only define the parameters of alcohol abuse and alcoholism, but explore the diverse fields of cause, diagnosis, treatment, and prevention as well as the biological and psychosocial factors that predispose people to alcohol abuse. Its clinical research studies are located on the NIH campus while the basic research activities are located in the Flow Laboratory and Park Building in Rockville.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTEs
FY 1991	$17,193,000	97
FY 1992	17,973,000	106
FY 1993	19,991,000	112
FY 1994	19,324,000	101
FY 1995	19,247,000	106

Rationale for the Budget Request

The FY 1996 request for intramural research is $19,815,000, an increase of $568,000 over the FY 1995 appropriation of 19,247,000.

For many Native American societies, alcohol has a destructive impact. Alcoholism accounts for more than 50% of deaths in some communities, and it degrades the quality of family and social relationships at many levels. NIAAA's intramural program currently is conducting large scale genetic studies of two Native American communities that have high rates of alcoholism. The intent of these projects is to identify alcoholism vulnerability genes and to learn more about the interaction of genetics and the environment which determines the risk for alcoholism. For comparison, a community in which the prevalence of alcoholism is dramatically lower, will be studied also. It is hypothesized that the tribe with low rates of alcoholism will show variations in identified alcoholism risk genes and will have lower incidences of post-traumatic stress disorder, spouse abuse and family violence, and substance abuse.

Another area of emphasis also addresses critical public health issues. Most individuals with antisocial personality disorder or intermittent explosive disorder are alcoholics and more than half of all violent crimes involve alcohol abuse. Early-onset alcoholics have much higher levels of risk-taking behavior and impulsivity than the general population. Intramural scientists are studying the brain mechanisms underlying these impulsive, risk-taking behaviors. In FY 1996 the correlation of brain neurotransmitter levels with impulse control and aggressiveness will be examined. NIAAA Intramural investigators will reveal the effects of functional alterations as well as structural damage associated with impulsivity by assessing metabolic activity in specific regions of the brain and impulsive behavior among certain patients. They will build on findings that alcohol use is an important factor linked to impulsive behavior to develop information that may ultimately prove useful in developing public health approaches to reducing random, unprovoked violent behavior and high risk sexual behavior.

One of the keys to discovering how alcohol addiction develops is understanding the molecular actions of alcohol in the brain. Recently, scientists in the NIAAA have made great progress in identifying the molecular sites of alcohol action in the central nervous system and the molecular mechanisms at those sites. Neurotransmitter receptors have been found to be molecular sites of alcohol action in the brain. Alcohol interacts with hydrophobic pockets on these receptor proteins to affect their function. These receptors mediate chemical communication between neurons in the brain, and are thus essential components of brain function. Identification of the molecular sites and mechanism of alcohol action in the brain is important because it provides a foundation for investigating the molecular basis of alcohol abuse and alcoholism.

Intramural scientists have shown in human alcoholics and animal models, that alcohol abuse leads to a loss of polyunsaturated lipids (fats) from a variety of tissues. Such losses are believed to be related to the tissue damage that occurs in almost every organ system in alcoholics, but particularly in the liver and brain. They have demonstrated a highly specific loss of the major polyunsaturated fatty acid, DHA, in nervous system tissues in cats and rhesus monkeys, who were given a "barely adequate diet" such as may be common in alcoholics. These results suggest that alcohol abuse has a similar effect on the nervous system in humans. The physiologically harmful effects of a loss in DHA include a deficiency in neurologic development. DHA, which is present in human milk, is not present in any formula available in the United States. These neural deficits would likely occur in alcoholics and in infants exposed to alcohol in utero, due to inadequate DHA. An intramural clinical project will study neurological development in infants who will receive a formula supplemented with DHA.

National Institute on Alcohol Abuse and Alcoholism

Research Management and Support

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part A Section 464H.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
133	$12,892,000	129	$13,017,000	127	$13,384,000	-2	+$367,000

The Research Management and Support activity supports overall management, planning, policy development, and coordination of the scientific programs and administrative functions of the Institute. Staff provide scientific direction, develop program announcements, support and monitor funded research projects, manage the review and award of grant and contract applications, organize conferences and related activities to promote new initiatives, develop alcohol-related policy analyses, and disseminate research results through a variety of publications, special reports, data systems, and other scientific documents.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTEs
FY 1991	$11,129,000	135
FY 1992	12,180,000	135
FY 1993	12,969,000	142
FY 1994	12,892,000	133
FY 1995	13,017,000	129

Rationale for the Budget Request

The FY 1996 request for research management and support is $13,384,000, an increase of $367,000 over the 1995 appropriation.

This activity will continue to provide leadership and guidance regarding the Institute's research programs and other scientific activities. Specifically, the research management and support activity (1) provides a continuing assessment of current Institute research activities in relation to broad research goals and objectives, and recommends changes basic alcohol research policy where needed; (2) administers the peer and objective review of grant applications and contract proposals; (3) coordinates and assures the development of, and adherence to, program policies and rules relating to Institute extramural activities; (4) assists the Director in obtaining expert advice to conduct evaluations of NIAAA research programs and scientists and (5) collects, abstracts, stores and disseminates program and scientific information on alcohol abuse and alcoholism. In addition, it supports and conducts conferences and workshops for the purpose of conveying up-to-date knowledge on alcoholism prevention, early intervention, treatment and rehabilitation to state and local government, the private and voluntary sectors, and others engaged in alcohol-related work.

Salaries and other operating costs included in the 1996 request are for staff who provide scientific direction and technical expertise in the development and implementation of the Institute's program as well as administrative support in areas of grant monitoring and review, management analysis, planning, budget, and personnel.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	8	7	8
Office of Planning and Resource Management	41	40	38
Office of Scientific Affairs	23	22	22
Office of Policy Analysis	5	5	5
Division of Clinical and Prevention Research	26	26	25
Division of Basic Research	15	15	15
Division of Biometry and Epidemiology	15	14	14
Division of Intramural Clinical and Biological Research	101	106	106
Total, NIAAA	234	235	233

	Average GS/GM Grade
1991	10.4
1992	10.6
1993	10.6
1994	10.8
1995	10.8
1996	10.8

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Program Administration
Detail of End-of-year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-5	2	2	2
ES-4	3	3	3
ES-3	1	---	---
Subtotal	6	5	5
Total - ES Salary	$647,300	$664,130	$681,397
GS/GM-15	20	19	19
GS/GM-14	40	40	40
GS/GM-13	17	18	18
GS-12	15	17	16
GS-11	19	23	22
GS-10	2	2	2
GS-9	18	20	20
GS-8	13	13	13
GS-7	20	24	24
GS-6	9	9	9
GS-5	3	4	4
GS-4	1	1	1
Subtotal	177	190	188
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	6	6	6
Senior Grade	8	7	7
Full Grade	2	2	2
Subtotal	16	15	15
Ungraded	32	32	32
Total permanent positions	193	200	199
Total positions, end of year	231	242	240
Total full-time equivalent (FTE) employment, end of year	234	235	233
Average ES level	4.0	4.0	4.0
Average ES salary	$107,883	$112,357	$113,481
Average GS/GM grade	10.8	10.8	10.8
Average GS/GM salary	$47,625	$46,084	$48,564

WEDNESDAY, MARCH 22, 1995.

FOGARTY INTERNATIONAL CENTER

WITNESSES

DR. PHILIP E. SCHAMBRA, DIRECTOR

STEPHANIE J. BURSENOS, DEPUTY DIRECTOR

ROBERT B. EISS, DIRECTOR, OFFICE OF INTERNATIONAL SCIENCE POLICY AND ANALYSIS

H. RICHARD MILLER, EXECUTIVE OFFICER

ELLA L. MENSER, BUDGET OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. Next we have the Fogarty International Center, Dr. Philip Schambra, the Director. Dr. Schambra, we are pleased to welcome you. We are dismayed that we only have about 25 minutes left of the morning session. We will do the best we can to allocate time within that short time frame, and please proceed and introduce the people at the table with you.

INTRODUCTION OF WITNESSES

Dr. SCHAMBRA. Thank you very much, Mr. Porter. It's a pleasure to be here again.

To my far left is Ms. Ella Menser, our Budget Officer. To her right is Mr. Richard Miller, the Executive Officer. To my left is Mr. Robert Eiss, Director, Office of International Science Policy and Analysis. To my right is Ms. Stephanie Bursenos, the Deputy Director, Dr. Harold Varmus, of course, and Mr. Bill Beldon. I'm so used to seeing Dennis Williams. [Laughter.]

OPENING STATEMENT

Mr. Porter, if I may, I'd like to submit my complete statement for the record and give a briefer version of my opening remarks.

Mr. Chairman, it's a pleasure to appear before you and the Members of this subcommittee to describe the mission, programs and accomplishments of the Fogarty International Center. As you well know, the Center was established in honor of a former chairman of this subcommittee, and in recognition of the importance of international scientific cooperation in the health priorities of our Nation.

Our mission for the American public is to provide leadership in confronting the most compelling international health threats and scientific challenges. Over this past year we have worked in concert with scientists throughout the country to develop a long-range plan to achieve the health research objectives of the Fogarty Center. The plan is focused on key global health threats of national importance.

Foremost is the need to protect our citizens from the health threats that emerge from worldwide ecological, social and demographic change, such as emerging infectious diseases and illnesses resulting from pollutants. As the international arm of the National Institutes of Health, the Fogarty Center carries forward an historic mandate to combat diseases of international origin.

In response to a 1988 Congressional mandate to implement an international program on AIDS, the FIC established research linkages between 13 U.S. and 40 foreign medical centers, in South America, Africa and Asia. Because of geographic differences in the characteristics of HIV and AIDS, international approaches are essential to develop vaccines and other prevention measures. In collaboration with U.S.-trained foreign scientists, American scientists have conducted international studies on the factors that have increased the risk of acquiring HIV.

New prevention measures are derived from such information and are applicable in the United States. One of the most promising research findings is that vitamin A may reduce the risk of HIV transmission from mother to child. This study was conducted in Malawi in cooperation with our grantees at Johns Hopkins University.

Based on the success of our program on AIDS and the priorities identified in our long-range plan, we propose to undertake new measures to strengthen the capacity of the United States to anticipate and prevent the spread of new infectious diseases. The AIDS virus is a sobering cautionary tale. It demonstrates the continuing risk to the American public of new or re-emerging infectious diseases, including Lyme disease in New England and the Midwest, Crypotosporidium in Wisconsin, Hantavirus pneumonia in the southwest, and Tuberculosis everywhere.

With the increasingly rapid mobility of individuals and populations, new infectious diseases can spread more quickly across borders and continents. Based on its international AIDS program, the FIC is forging scientific linkages between U.S. research institutions and those regions of the world where new infections are likely to arise due to changing population patterns and encroachments on wilderness.

Equally insidious health risks are presented by rising concentrations of pollutants, particularly in countries undergoing rapid industrialization. These hazards are transnational in scope, and underscore the importance of international cooperation to identify and prevent environmentally-induced diseases.

Through the Fogarty Center's International Program on Environmental and Occupational Health, established, I might point out, at the encouragement of this committee, the United States will work cooperatively with regions of the world burdened with relatively high contamination levels. The objective is to study the effects of environmental agents on human health and to develop new interventions. The program is a joint effort of the Fogarty Center, the National Institute of Environmental Health Sciences and CDC's National Institute for Occupational Safety and Health.

Environmental degradation, including the destruction of tropical rain forests, will also diminish the discovery of new medicines. In the United States, one quarter of all pharmaceuticals are substances extracted from plants. Another 13 percent are derived from microorganisms. However, only a modest fraction of the world's biological resources has been examined for therapeutic potential.

In partnership with other NIH research Institutes, the National Science Foundation and the U.S. Agency for International Development, the Fogarty Center supports and administers the International Cooperative Biodiversity Groups Program. Its purpose is to discover new drugs from the earth's biological diversity while advancing ways to preserve important ecosystems and promote economic growth through sustainable agriculture. Research is conducted by consortia of American and foreign scientists from universities, foundations and pharmaceutical firms who share expertise and resources.

The emergence of new infectious diseases, increased human exposure to pollutants, and the destruction of natural ecosystems are all related to demographic changes. Therefore, in cooperation with the National Institute of Child Health and Human Development, the Fogarty Center has launched an International Program on Population and Health. The purpose of this program is to enable American universities to cooperate with scientists in developing nations to improve reproductive health and better understand the social and behavioral determinants of population change.

The Fogarty Center also works to prepare the current and future generation of American scientists to work effectively within a global environment. With the support of NIH's Office for Research on Minority Health, the Fogarty Center has launched a program to enable African American, Hispanic American and Native American students to pursue research and training at academic institutions on four continents. The goal is to encourage students from groups underrepresented in the biological research professions to pursue research careers through the stimulus of international programs.

FIC also serves as the NIH link with the Department of State, international organizations and foreign ministries. In support of the Middle East peace process, the FIC worked with the State Department to launch a cooperative program among Arab, Israeli and American scientists to assess the environmental risks of pesticides in the region. The FIC also conceived and helped develop a proposal for the creation of a Council on Science and Technology for the Americas, or COSTA, which was adopted at the Summit of the Americas in Miami this last December.

The NIH remains a world leader in research, but we have many allies and much to learn from them. Today, new discoveries and techniques may be pioneered in foreign laboratories as well as our own. Increasingly, American scientists must know and interact with their colleagues in the "global laboratory". In a world fragmented by ethnic conflict, health research reminds us of our common kinship, while the universal benefits that derive from international cooperation advance our national scientific goals, humanitarian interests and foreign policy.

Thank you, Mr. Chairman. The Fogarty International Center's budget request for fiscal year 1996 is $15,267,000, and I'd be pleased to respond to any questions you or members of the Subcommittee may have.

[The prepared statement and biography of Dr. Philip Schambra follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
John E. Fogarty International Center for Advanced Study in the Health Sciences

Mr. Chairman, it is a pleasure to appear before the Subcommittee to describe the mission, programs and accomplishments of the Fogarty International Center (FIC). The Center was established in honor of a former chairman of this Subcommittee, and in recognition of the importance of international scientific cooperation in the health priorities of our nation. Our mission for the American public is to provide leadership in confronting the most compelling international health threats and scientific challenges.

Over this past year, we have worked in concert with scientists throughout the country to develop a long-range plan to achieve the health research objectives of the FIC. The plan is focused on key global health threats of national importance. Foremost is the need to protect our citizens from the health threats that emerge from worldwide ecological, social and demographic change, such as emerging infectious diseases, and illness resulting from pollutants. As the international arm of the National Institutes of Health, the FIC carries forward an historic mandate--to combat diseases of international origin.

In response to the 1988 Congressional mandate to implement an international research and training program on the epidemiology of AIDS, the FIC has established research linkages between 13 U.S. and 40 foreign medical centers in South America, Africa and Asia. Because of geographic differences in the biological and epidemiological characteristics of HIV/AIDS, international approaches are essential to develop vaccines and other prevention measures.

In collaboration with U.S. trained foreign scientists, American scientists have conducted international studies on the factors that enhance the risk of acquiring HIV. New prevention measures are derived from such information and are applicable in the United States. One of the most promising research findings, reported in Lancet, is that Vitamin A, a key micronutrient, may reduce the risk of HIV transmission from mother to child. This study was conducted in Malawi in cooperation with Johns Hopkins University. A second study, reported in Science, has examined the factors that prolong the life of Africans infected with the AIDS virus. In Senegal, some individuals infected with HIV 2--a less potent form of the virus--survive dramatically longer than individuals infected with the more common virus type, HIV 1. With these clues, scientists are seeking ways to better understand and ultimately influence the immune process to yield longer survival times.

Based on the success of our program on AIDS, and the priorities identified in our long-range plan, we propose to undertake new measures to strengthen the capacity of the United States to anticipate and prevent the spread of new infectious diseases. The AIDS virus is a sobering cautionary tale. It demonstrates the continuing risk to the American public of new or re-emerging infectious diseases, including Lyme disease in New England and the Midwest, Cryptosporidium in Wisconsin, and lethal Hantavirus pneumonia in the Southwest.

With the increasingly rapid mobility of individuals and populations, new infectious diseases can spread more quickly across borders and continents. Based on its international AIDS program, the FIC is forging scientific linkages between U.S. research institutions and those regions of the world where new infections are likely to arise, due to changing population patterns and encroachments on wilderness. Perhaps if an international "sentinel" system had existed two decades ago--capable of detecting new patterns of infectious disease--we may have limited the scope of the AIDS epidemic.

Equally insidious health risks are presented by rising concentrations of industrial and chemical pollutants, particularly in countries undergoing rapid industrialization. These hazards are transnational in scope and underscore the importance of international cooperation to identify and prevent environmentally-induced diseases. The radioactive fallout from Chernobyl, for example, was a health hazard in neighboring countries.

Through the FIC International Training and Research Program on Environmental and Occupational Health, the United States works cooperatively with regions of the world burdened with relatively high contamination levels. The objective is to study the effects of environmental agents on human health and to develop new interventions. The program is a joint effort of the Fogarty Center, the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention.

Environmental degradation, including the destruction of tropical rain forests, will also diminish the discovery and development of new medicines. In the United States, one-quarter of all pharmaceuticals are substances extracted from plants. Another 13 percent are derived from microorganisms. However, only a modest fraction of the world's biological resources has been examined for therapeutic potential.

In partnership with other NIH research institutes, the National Science Foundation (NSF), and the U.S. Agency for International Development (USAID), the Fogarty Center supports and administers the International Cooperative Biodiversity Groups Program. Its purpose is to discover new drugs from the earth's biological diversity while advancing ways to preserve important ecosystems and promoting economic growth through sustainable agriculture. Research is conducted by consortia of U.S. and foreign scientists from universities, foundations and pharmaceutical firms, who share expertise and resources.

The emergence of new infectious diseases, increased human exposure to pollutants, and the destruction of natural ecosystems are all related to demographic changes. In cooperation with the National Institute of Child Health and Human Development, the FIC has launched an International Training and Research Program on Population and Health. The purpose of this program is to enable American universities to cooperate with scientists and health professionals in developing nations, to improve reproductive health and to better understand the social and behavioral determinants of population change.

In addition to programs that address global health threats, the FIC supports investigator-initiated grants and fellowship programs to enable the U.S. to benefit from innovation, expertise and special resources throughout the world.

The FIC Scholars-in-Residence Program brings some of the world's leading scientists to the NIH campus to conduct advanced study in concert with NIH intramural scientists. Over the past year, one Scholar has examined the genetic changes in the influenza virus which enable it to elude vaccine immunity. This new technology will lead to more rapid development of flu vaccines when the threat of a new epidemic appears.

Through the program of Fogarty International Research Collaboration Awards (FIRCA), American scientists cooperate with counterparts in regions of the world which present new opportunities due to democratic change. Examples include American and Hungarian scientists who have done research on the metastasis of tumors and discovered the biochemical steps that result in the migration of tumor cells to other regions of the body. One enzyme, known as 12 lox, appears to activate key events in cancer metastasis. This enzyme is now a potential target for new anti-cancer drugs.

A cooperative study with scientists in the Slovak Republic has resulted in the isolation of a gene that determines the cellular receptor, or "docking place" of bovine leukemia virus, one of a family of "retroviruses" which includes HIV. This finding may have implications for the development of a retroviral vaccine or other strategies to assist the immune system to fight infection.

The Fogarty International Center also works to prepare the current and future generation of American scientists to work effectively within a global environment. With the support of NIH's Office for Research on Minority Health, the FIC has launched a program to enable African American, Hispanic American and Native American students to pursue research and training at academic institutions on four continents. A goal is to encourage students from groups underrepresented in the biomedical research professions to pursue research careers through the stimulus of international programs.

Recognizing the growing importance of biomedical research in Japan and the need for U.S. scientists to learn firsthand about scientific advances in that country, the FIC supports American graduate students to conduct research in Japan. The Summer Institute in Japan Program, funded jointly by the Japanese government, the Fogarty Center and the National Science Foundation, transfers basic innovations and research technologies from Japanese laboratories to the United States.

FIC also serves as the NIH link with the Department of State, USAID, the international component of the White House Office of Science and Technology Policy, and international organizations and foreign ministries. In support of the Middle-East peace process, the FIC worked with the Department of State to launch a cooperative program among Arab, Israeli and American scientists to assess the environmental risks of pesticides in the region. Through a bilateral agreement known as the U.S.-Japan Common Agenda, FIC contributed to a major shift in Japanese foreign aid toward support for development of childhood vaccines, combatting AIDS, and the eradication of polio in Asia. The FIC also conceived and helped develop a proposal for the creation of a Council on Science and Technology for the Americas (COSTA), which was adopted at the Summit of the Americas in Miami. The COSTA will increase collaboration among the scientific communities of the Americas.

FIC efforts to coordinate its programs with NIH research institutes and other government agencies have been an effective strategy for optimizing the use of Federal resources. In addition, over the past year, the FIC downsized selected programs to refocus resources on our most compelling priorities.

The NIH remains a world leader in research, but we have many allies and much to learn from them. Today, new discoveries and techniques may be pioneered in foreign laboratories as well as our own. Increasingly, American scientists must know and interact with their colleagues in the "global laboratory". In a world fragmented by ethnic conflict, health research reminds us of our common kinship, while the universal benefits that derive from international cooperation advance our national scientific goals, humanitarian interests, and foreign policy.

Thank you Mr. Chairman. The Fogarty International Center's budget request for FY 1996 is $15,267,000. I will be pleased to answer any questions members of the Subcommittee may have.

CURRICULUM VITAE

Name: SCHAMBRA, DR. PHILIP E.

Date & Place of Birth: November 8, 1934. Saginaw, Michigan

EDUCATION:

1956	B.A., Rice University
1961	Ph.D., Yale University
1961-1963	Postdoctoral, Institut für Strahlenbiologie, Karlsruhe, Germany
1964-1966	Postdoctoral, University of California, Berkeley

Professional History:

1956-1958	Research Assistant, Biophysics Department, Yale University.
1958-1961	Predoctoral Fellow, National Cancer Institute, Biophysics Department, Yale University.
1961-1963	Research Associate, Institut für Strahlenbiologie, Karlsruhe, Germany.
9/64-2/65	Instructor, Department of Medical Physics, University of California, Berkeley.
1964-1967	Research Biophysicist, University of California, Berkeley. NASA Research Fellowship.
1966	Laboratory Director, National Science Foundation Summer Institute in Radiobiology, University of California, Berkeley.
1967-1968	Grants Associate, National Institutes of Health.
1968-1971	Budget Examiner, Office of Management and Budget, Executive Office of the President.
1971-1974	Staff Member, Council on Environmental Quality, Executive Office of the President.
1974-1980	Associate Director for Interagency Programs, National Institute of Environmental Health Sciences, NIH.
1980-1984	Chief, International Coordination and Liaison Branch, Fogarty International Center, NIH.
1984-1988	Science Attache and PHS International Health Representative, U.S. Embassy, New Delhi, India.
1988-Present	Director, Fogarty International Center, National Institutes of Health.

Honors and Awards:

1984	NIH Merit Award
1989	PHS Superior Service Award
1982-1994	Outstanding Performance Ratings

Mr. PORTER. Thank you very much, Dr. Schambra.

I am going to have to forego my own questions for a few minutes, because I have a live radio interview I have to do. I'm going to call on Mr. Stokes, and ask Mr. Stokes to yield at an appropriate point to Ms. Pelosi, and then I'll be back.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Schambra, nice to see you again.

Dr. SCHAMBRA. Good to see you again, Mr. Stokes.

AIDS

Mr. STOKES. Thank you very much.

I noticed, Dr. Schambra, on page one of your formal testimony, you mentioned that in response to the 1988 Congressional mandate to implement an international research and training program on the epidemiology of AIDS, the FIC has established research linkages between 13 U.S. and 40 foreign medical centers in South America, Africa, Asia. And because of geographic differences in the biological and epidemiological characteristics of HIV–AIDS, international approaches are essential to develop vaccines and other prevention measures. How far away are we from developing vaccines and other preventive measures?

Dr. SCHAMBRA. Well, certainly as far as preventive measures are concerned, I think that we are making some very important inroads on this problem. Vaccines are much more complicated and I believe that Dr. Varmus and Dr. Paul have addressed or will address that issue.

Our program is really aimed at preparing the groundwork for the eventual trials in the field of new interventions, therapeutics and/or new vaccines that will be developed in our laboratories and in laboratories of other countries of the world.

In some cases, there are some preliminary trials of vaccines going forward, as in Thailand, for example, where the U.S. Army, working with the Thai military, is in the process of testing vaccines believed to have some protective potential. But how soon it will be before we get around to testing vaccines in other countries I think depends on the speed and the success of the research and the preliminary trials that we expect ultimately will take place even within our own country.

Mr. STOKES. You mentioned to us in your testimony that one of the most promising research findings reported in Lancet is that vitamin A, a key micronutrient, may reduce the risk of HIV transmission from mother to child. Are there other prevention measures of that note?

Dr. SCHAMBRA. That's been a very interesting and striking discovery that came out of studies that were done by scientists from Johns Hopkins in Malawi who noticed a correlation between the levels of vitamin A in pregnant women and ultimately the outcome of the birth of a child with or without HIV. It was found that the higher the levels of vitamin A, the less likelihood there was of transmission of the HIV virus to their offspring. In fact, this result has led us to organize and implement therapeutic intervention trials for HIV where we would give pregnant women, who are HIV-infected, supplemental doses of vitamin A in the hopes of reducing the chances of transmission of HIV to their offspring.

Some other very interesting results which have surfaced through other studies conducted by Harvard University scientists in Senegal have to do with the difference in the infectivity and in the clinical outcome of individuals infected with different forms of the HIV virus. HIV–1 is the common form in the United States and much of the rest of the world. HIV–2 is more prominent in parts of West Africa, including Senegal and the Ivory Coast. By studying the differences between these two viruses, we may gain important clues about how to impede the pathogenic process of HIV–1.

Mr. STOKES. I noted that you're finding some very interesting things in terms of a longer survival rate amongst those who are infected with either HIV–1 or 2. Do we know why?

Dr. SCHAMBRA. Apparently, those individuals who are initially infected with HIV–2 appear to show some protective effect against subsequent infection with HIV–1. And there may be something that can be learned out of that. If we understand why HIV–2 is less harmful to the human body than HIV–1, that may be transferable then to the development of an appropriate vaccine or therapeutic in the treatment of HIV–1 infected individuals.

This, I think, exemplifies the fact that there are definite benefits to be derived from studying these types of infections in foreign populations. We would not be able to do this within the United States, for example.

MINORITY RESEARCH SUPPORT

Mr. STOKES. That sounds very exciting, really.

Let me ask you this. About a year or so ago, I had occasion to come out to your Institute and attend and participate in what to me was a very educational and enlightening experience in terms of participation of minorities in international research. This was a program that your Institute had established, along with Dr. John Ruffin in the Office of Minority Health Research. Can you bring us up to date in terms of that program and what's being done?

Dr. SCHAMBRA. I'd be pleased to do so, Mr. Stokes. It is, I think, one of the feathers in our cap, and we're very proud of it. You may recall that we made 15 awards in 1993, and then 11 new awards this last year for a total of 26 grants involving 48 U.S. colleges and universities, including 16 historically black colleges and universities.

The purpose of these grants is to provide minority Americans underrepresented in the biological sciences the opportunity for an international experience—to experience the thrill of science, of biomedical science in particular—and to learn the importance and advantages of international linkages in advancing the field of science, not just as a national enterprise, but as a global enterprise.

To bring you up to date, through this year, we will expect more than 300 students and faculty to be going abroad to over 50 countries. We have held a second network meeting of the principal investigators from the different grantee institutions involved to meet to share experiences, problems, and successes, even bringing their students so that the entire network, the entire community, will benefit.

One of the very gratifying elements of this program has been the willingness of the principal investigators to reach out to other colleges and universities to invite their minority students to participate in this program, and eventually in this fashion we would like to see this rather modest program, at least in terms of the numbers of institutions involved, extend throughout the United States.

Mr. STOKES. I certainly want to commend you for having followed through relative to this initiative, and the one we have discussed here at the hearing. You made a commitment to follow through, and you did. And I'm very pleased with the results of what you've been able to do in that area.

Dr. SCHAMBRA. Thank you.

Mr. STOKES. Thank you.

I'm pleased to yield to my colleague, the distinguished lady, Ms. Pelosi.

NEW AND EMERGING INFECTIOUS DISEASES

Ms. PELOSI. Thank you.

I was fascinated by your testimony. I have not had the opportunity to visit, but certainly consider the work that you do very important, and appreciate your testimony this morning. You said in your written statement that perhaps if an international sentinel system had existed two decades ago capable of detecting new patterns of infectious diseases, we may have limited the scope of the AIDS epidemic.

In light of that statement, I wonder if you could comment on the impact of the rescission bill which cut $3 million, or half of the increase for funding to respond to an IOM report on ways of controlling new and emerging infectious diseases. That report, I'm sure you know, placed a great deal of emphasis on international early surveillance efforts.

So to what extent do you think this rescission will affect——

Dr. SCHAMBRA. Was this in the CDC rescission?

Ms. PELOSI. IOM. That's CDC, yes.

Dr. SCHAMBRA. Well, there's no question that the issue of new and re-emerging infectious diseases, as most strongly exemplified by the experience we've had now over the past dozen years with HIV and AIDS, is becoming an increasingly important issue, and one that, individually and collectively, our agencies are not paying enough attention to.

Certainly within our own sense of priorities in the Fogarty International Center, and as an outgrowth of our long-range plan, we have identified the expansion of our role in AIDS internationally to also encompass more broadly new and re-emerging infectious diseases, Tuberculosis being a familiar one, the Hantavirus respiratory syndrome a less familiar one, and even more lethal viruses, such as the Lassa and Ebola, lurking around the corner. We've identified these as issues that we must pay attention to, certainly from our point of view, if the opportunity arises, and it will arise within the development of the President's budget. We hope to be able to put forward a new initiative in the future that will expand our activities in exactly this area.

Ms. PELOSI. Is that, the list that you mentioned, inclusive of what you see out there? Are any of those things we should be fear-ing and dreading that could emerge health-wise? We don't know the unforeseen, but I'm just asking what you see.

Dr. SCHAMBRA. Well, that's right. I don't think anyone could have foreseen the AIDS epidemic, for example. One can look back at the history of this century, to the killer flu epidemic around the time of the First World War, which killed tens of millions of people worldwide. Will the influenza virus mutate again to come back to be as lethal as it was then? And of course, we had the swine flu scare some years ago, that sort of speaks to that issue as well.

We don't know what the future brings, but certainly the best way to be prepared for it is, number one, by doing the basic research that all of the Institutes are involved in so that we understand the way disease processes work, especially those caused by pathogens—viruses, bacteria and so on in the environment. And then, two creating a cadre of individuals not only trained within the United States but in developing countries and other countries around the world where many of these outbreaks are likely to originate, so we can be prepared to not only anticipate them, but to deal with them in their earliest possible stages.

COOPERATING EFFORTS

Ms. PELOSI. To what extent does your agency cooperate with the CDC in these efforts?

Dr. SCHAMBRA. Well, the Fogarty Center worked very closely with the CDC as they developed their own strategic plan on this initiative. We had the opportunity to comment extensively on their plan and we consulted them when we did our own long-range plan. We likewise took advantage of CDC's expertise in developing it.

We are right now, under Dr. Varmus' leadership, proposing an international meeting with our counterparts in France and Britain, along with the Centers for Disease Control, to begin to focus on specific activities that we might undertake on the African continent. We have not only common interests and a number of currently active programs, but a lot of concern about the health status of the people on the continent and what might evolve, in fact, from that continent in the way of new diseases.

Ms. PELOSI. Well, I appreciate that, and I do think we have a responsibility in our country to take a lead on this issue. And of course, for what it does for us, but also with the responsibility we have internationally.

In your closing statement you said that in a world fragmented by ethnic conflict, health research reminds us of our common kinship, while the universal benefits that derive from international cooperation advance our national scientific goals, humanitarian interests and foreign policy. And earlier, you referenced your work on the environmental causes of illness.

I can't let the opportunity pass without saying how blessed we are to have our Chairman, because he has been a leader in every one of these areas. He serves as Chair of this committee and is an active participant in our Foreign Operations Committee on these issues. He is also Human Rights Caucus Chairman and a leader in international environmental issues as well. So I feel that we have very good judgment at the helm and leadership on these issues. I didn't want the opportunity to pass by and not make this statement about you, Mr. Chairman.

Dr. SCHAMBRA. I couldn't agree with you more, Ms. Pelosi.

Mr. PORTER. Ms. Pelosi, you've got to be here every day. [Laughter.]

Mr. PORTER. Actually, it has been one of my great pleasures in serving in the Congress to work with you and under your leadership in all of these areas. Because you have been more forthright than any other Member of Congress in providing that kind of leadership. And it's been a real pleasure to work with you, and I want to continue to do so.

Ms. PELOSI. Thank you, Mr. Chairman.

BIODIVERSITY

Mr. PORTER. Dr. Schambra, you know I've been interested in your work on biodiversity. And I wonder if you can tell us what resources you and other agencies are allocating to the international cooperative biodiversity groups and what has been the output of the efforts so far? Have any promising substances been identified that are ready for drug testing?

Dr. SCHAMBRA. Mr. Porter, you'll recall that about a year ago we funded five grants with funds from not only the Fogarty International Center but four NIH Institutes—the National Cancer Institute, the National Heart Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Mental Health—and combined with funds from the National Science Foundation (NSF) and the U.S. Agency for International Development (USAID) to start this rather unique program. You will recall that the impetus for this joint effort was to combine three overlapping and hopefully mutually supporting interests; the NIH's interest in developing pharmaceutical products from the natural products in the biosphere, the National Science Foundation is interest in conserving and protecting biodiversity, and the Agency for International Development's interest in seeing the economic development of countries in which many of these products are found.

I think an important distinguishing factor about these cooperative biodiversity groups is that it includes experts from the U.S. and abroad, from academia and industry, and local populations and governments. I am pleased to report to you that the five groups are now all active, working in seven countries, six in Latin America and one in Africa. To date, they've collected over 1,200 species of plants and insects and 25 samples have been found to show some activity against, for example, cancer, tuberculosis, viruses and malaria. We hope some of these will eventually turn into commercial products. Of course, we won't know that for some time, but I'd say this is quite a remarkable achievement in such a short period of time into the program, and we're looking forward to the next couple of years.

You asked about the level of funding. Currently, the Fogarty Center is putting in about a million dollars a year, while the other agencies are putting in a million and a half dollars. So it's roughly $2.5 million a year at the current level.

Mr. PORTER. Are you getting support from the countries involved for your efforts to promote economic growth through sustainable agriculture?

Dr. SCHAMBRA. Yes, at least the anecdotal evidence that I'm familiar with indicates a very positive reaction. In fact, I think one of the strengths of this program is that we approach these countries' governments, and the indigenous peoples where many of these natural products are found, with the idea that they have an economic and social and cultural interest in what comes out of it, and not just simply in providing raw materials for exploitation by developed countries of the world. We've been very pleased with the very positive reaction we've had to the constellation of issues and priorities that we're trying to reflect through the Cooperative Biodiversity Groups Program.

DOWNSIZING

Mr. PORTER. I've got a tough question for you. With pressures to downsize—and you know I'm a great fan of the Fogarty Center—some might look at the Fogarty Center and wonder if its mission is secondary to the NIH core function. How would you respond to those who might believe international efforts are a luxury that we can no longer afford in this difficult budgetary environment?

Dr. SCHAMBRA. Well, I'm glad you asked that question, Mr. Porter, because in fact, it's something that we've been thinking about for the last several years, and not in the least through the impetus of the need to develop a long-range plan. As we saw the end of the Cold War, as we look back on 25 years of history and sometimes programs that we had been running for more than 30 years, we realized it was a time to really take a look at our role within Government, within NIH, within the Department of Health and Human Services. I'd say that recent events in downsizing Government and REGO–1 and 2 have confirmed our need to do that, and in fact given us a strong impetus to do that.

As we look at our distinctive role within the NIH and within the Government, I would cite three particular characteristics that we bring to the biomedical science field.

First of all, our work has a global perspective. And by that I mean that unlike other NIH components which have responsibility for a particular disease or set of related diseases or an organ system, the Fogarty Center focuses more broadly on diseases and conditions which we have defined as representing global health threats affecting the world's population, including Americans. Here I'm referring obviously to AIDS and the broader problem of new and reemerging infectious diseases, to environmental pollution, global climate change and the impact on biodiversity and the natural environment, and the population explosion, which is at the root of many of these problems that we face. So that global perspective, I'd say, is the first distinctive characteristic that we bring to the table.

Secondly, our work is integrative in its nature in terms of recognizing the relationships between these global health threats. For example, increased population leads to increased pollution and increased industrial development. Increased population puts pressure on the environment, and these issues increase the possibility of encountering new pathogens leading to new diseases. We also help integrate the domestic priorities of the Institutes of NIH, which we work very closely with, with foreign research centers—our Biodiversity program is a good example of that. Also, by integrating foreign scientists into these global efforts, we all share the knowledge, resources and costs.

Finally, I would say that what we bring to the table is a strong support role for American foreign policy. Combatting diseases abroad is not only humanitarian, but it promotes economic development in those countries that benefit from lower levels of morbidity and mortality, and contributes to political stability in those countries, as well as protecting Americans from the import of diseases.

That's how I would characterize our distinctive contributions to this Government.

Mr. PORTER. I think that was an excellent answer, and I very much appreciate your testimony. I wish we had additional time to ask additional questions. Unfortunately, we've run out of time, and I'll have to put my remaining questions, and others will also, in the record.

But we appreciate the excellent job you're doing at the Fogarty Center, Dr. Schambra, you and your staff. And we're very supportive of your work. I think it is of tremendous importance, not only to the American people, but to all of humankind. And we appreciate your testimony today. Thank you so much.

Dr. SCHAMBRA. Thank you very much.

Mr. PORTER. We will stand in recess until 2:00 p.m.

[The following questions were submitted to be answered for the record:]

Questions Submitted by the Subcommittee

FUNDING FROM OTHER SOURCES TO FIC INITIATIVES

Mr. Porter: Identify 1995-96 funding contributed by other agencies to FIC initiatives.

Dr. Schambra: Anticipated contributions from other agencies, including other NIH/ICD co-support, for FIC's major initiatives follow:

	FY 1995	FY 1996
	($ in Thousands)	
Population and Health		
National Institute of Child Health and Human Development	$200	$200
Environment and Occupational Health		
National Institute of Environmental Health Sciences	$150	$150
National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention	$150	$150
International Cooperative Biodiversity Groups Awards		
National Science Foundation	$500	$500
US Agency for Int'l Development	$500	$500
National Institute of Allergy and Infectious Diseases	$100	$100
National Cancer Institute	$400	$400
National Institute of Mental Health	$50	$50
Minority International Research Training Program		
Office of Research on Minority Health, NIH	$6,000	$6,000
	$8,050	$8,050

FIC LONG-RANGE PLAN

Mr. Porter: Dr. Schambra, during the past year you have developed a long-range plan for your Center. Can you describe the four major goals you have identified and the areas you have targeted for future expansions if resources permit.

Dr. Schambra: Over the past year, the FIC completed a comprehensive program plan, in consultation with the FIC Advisory Board and a representative group of scientists from academia, industry and relevant Federal agencies. As an outcome of these collective efforts, we have identified key scientific, human resource and science policy goals and priorities.

The plan builds effectively on past programmatic strengths and identifies important new directions for FIC. Emphasis is placed on global health threats that require international cooperation, and programs that promote long-term scientific cooperation and enable NIH grant recipients to benefit from unique or specialized resources abroad. Current and prospective training needs are addressed through fellowships for young American investigators and scientists from less developed regions key to international research efforts. In addition, international policy issues are identified that require continuing analysis in support of NIH programs.

GOALS

Four broad goals will be pursued:

- To Mobilize International Research Efforts Against Global Health Threats

A key role of the FIC is to protect American citizens, and citizens of other nations, from health threats that emerge from ecological, social and demographic change on a global scale. The plan carries forward a founding mandate of the NIH--to combat health threats of international origin.

- To Advance Science through International Cooperation

The FIC fosters discovery through the support of international cooperation across the continuum of biomedical science. The plan advances the "cutting-edge" of science through cooperation in strategically important geographic regions, and through the support of advanced studies in emerging fields of science.

- To Develop Human Resources to Meet Global Research Challenges

FIC has a significant role to play in preparing the current and future generations of biomedical scientists to function and excel in a global environment, and to assist them to work interdependently to meet global health challenges that exceed the capabilities and resources of any one nation.

- To Provide Leadership in International Science Policy and Research Strategies

FIC will exercise leadership by advancing NIH research needs and opportunities in a global context, and by analyzing international policy issues that affect the course and conduct of biomedical science. The plan identifies several areas for emphasis. These include international strategies to share research costs and pool efforts toward mutual scientific goals.

NEW AND EXPANDED ACTIVITIES

If additional resources were available, FIC's first priority would be to broaden research support related to combating global health threats. The FIC HIV/AIDS research and training effort, launched in 1988, presents a successful paradigm to respond to other global health threats. At present, FIC is the largest single source of HIV/AIDS research training for scientists from developing nations. The program has increased research capacity in HIV/AIDS in over 50 developing nations. It has helped develop a cadre of scientists to launch national prevention programs and participate in future international AIDS vaccine trials and the testing of other interventions. And, it has enabled U.S. scientists to conduct important international studies on HIV/AIDS epidemiology and risk factors.

FIC's objective is to have a similar cadre of scientists in the fields of emerging infectious diseases, population and environment, as it has with HIV/AIDS. This would demonstrate a compelling leadership role for the United States in international health. It would train a meaningful numbers of scientists in partnership with U.S. universities, who would retain their close ties to the U.S.--many of whom will represent the future scientific leadership of these countries.

There are important synergisms among habitat destruction, infectious disease and population densities. For example, climate change due to stratospheric ozone depletion may enable pathogens to expand their range. With expanded support, FIC would explore interdisciplinary approaches that advance knowledge in support of public health, social and environmental policies at the international level and in participating countries.

With additional resources, the FIC also would extend international research and training opportunities to American scientists at the formative stages of their professional training. The FIC would provide new opportunities to pre- and postdoctoral scientists (within five years of obtaining a professional degree) who have demonstrated outstanding research skills. These opportunities would enable American researchers to benefit from collaborative studies at centers of scientific excellence abroad, to contribute to global research efforts through project-based partnerships with research centers in developing nations, and to seed longer term associations that continue into their professional careers.

These awards are envisioned as the biomedical science equivalent of career development scholarships supported under the Marshall, Fulbright and Rhodes endowments. They are intended to enrich the intellectual and cultural perspective of America's future scientific leaders.

DOWNSIZING ISSUES

Mr. Porter: Your testimony indicates that you have downsized selected programs to refocus your priorities. Which programs have been reduced?

Dr. Schambra: We have terminated the Health Scientist Exchange Program with a number of countries, and reoriented the International Research Fellowship Program to support scientists only from developing countries, thus reducing the number of awards in the process. We have also reduced the size of our administrative apparatus by consolidating five branches into three divisions.

PROGRAM ON POPULATION AND HEALTH

Mr. Porter: You are beginning an international research and training program on population and health. How many trainees are involved in this effort, and can you give us examples of the types of research they may become involved in? Are any particular countries targeted in this initiative?

Dr. Schambra: Following completion of the FIC long-range plan, the FIC and the National Institute of Child Health and Human Development (NICHD) discussed the potential role of NIH in meeting the global challenge of sustainable population growth.

As an outcome of these discussions, we have launched an international research and training program on population and health. The intent is to transfer research skills and knowledge to enable developing nations to improve reproductive and neonatal health care, family planning services and demographic capabilities. The program also will assist developing nations to better understand the social and behavioral determinants of population change, in support of policies that are responsive to cultural needs.

The program is based on a successful international program model established by FIC to combat HIV/AIDS. International research and training grants will be awarded competitively to U.S. universities with population research and training programs supported by NIH. These funds will enable American faculty to enter into partnerships with scientists and institutions in developing nations. Emphasis will be placed on the training of young scientists from developing nations in the biomedical, behavioral and demographic sciences, and cooperative studies conducted in-country on reproductive and maternal health priorities.

The Request for Applications for this program was issued on November 18, 1994, with an applications receipt date of April 20, 1995. After standard peer review, funding decisions will be made by September 30, 1995. It is anticipated that six to seven awards will be made, with individual awards of up to $150,000 in total costs for the first year.

While the most important factor in making funding decisions will be scientific quality rather than target countries, attempts will be made to ensure broad geographic distribution among developing countries of Africa, Asia and the Pacific region, the Middle East, and Latin America and the Caribbean. Emphasis will be placed on collaborative activities with countries and regions where population growth adversely impacts public health, the environment, and economic progress.

Mr. Porter: Is the Fogarty program coordinated with the population and health activities of the World Health Organization?

Dr. Schambra: A component of this program will be the formation of a network of investigators conducting international research in population and health. This network will provide a mechanism for coordination and information-sharing among investigators and with the population activities of the World Health Organization, as well as activities resulting from the U.N. International Conference on Population and Development, held in Cairo in September of 1994.

PROGRAM ON ENVIRONMENT AND HEALTH

Mr. Porter: You are also starting an international research effort on environment and health. While the goal of training environmental health scientists is admirable, are the countries with severe environmental problems likely to have the financial resources to act on the research findings?

Dr. Schambra: Environmental toxins are increasingly recognized as important factors in the etiology of cancer, respiratory disease, kidney disease, autoimmune disorders, and developmental and behavioral disorders--diseases of interest to nearly all components of the NIH. These hazards are transnational in scope and underscore the importance of international cooperation to identify and validate biological markers for environmentally-induced diseases and to develop interventions to prevent diseases in populations with known toxic exposures, both in the environment and the workplace.

The FIC's International Training and Research in Environmental and Occupational Health Initiative is designed to improve epidemiologic and related research capabilities in countries affected by environmental and occupational health problems. This initiative complements ongoing domestic research by establishing cooperative relationships between U.S. and foreign researchers. These collaborations aid in the standardization and coordination of complex international studies. Epidemiological data collected and interventions tested in such studies improve understanding of health risks both at home and abroad.

While less developed countries may have limited resources with which to respond to environmental and occupational health problems, the information generated through these studies should enable local authorities to make the best use of the resources that are available to them. Epidemiological studies that pinpoint the worst-affected regions will assist local officials to take ameliorative action. Local researchers trained through this initiative will be able to suggest the simplest and most appropriate solutions based on broad-based training in relevant fields and extensive U.S. contacts.

The program will increase global research capacity related to environmental and occupational hazards, including expertise in epidemiology, industrial hygiene, atmospheric chemistry, toxicology, risk assessment, hazardous waste disposal and biomechanics. It will establish research and training partnerships in regions of the world which present unique opportunities to study the effects of environmental agents on human health and to develop new interventions. The potential adverse health effects resulting from exposures to environmental chemicals are often first identified in populations of other countries. These include studies on the carcinogenicity of dioxin, the neurotoxic effects of methylmercury and the reproductive toxicity of polychlorinated biphenyls.

SENTINEL SYSTEM FOR INFECTIOUS DISEASE

Mr. Porter: One of your areas of emphasis is infectious disease. The Institute of Medicine has talked about developing a sentinel system for infectious disease, which is likely to be very expensive to establish. Does any sort of global network now exist that could be developed into some form of sentinel system?

Dr. Schambra: Yes, many experts believe that through the FIC AIDS International Training and Research Program a cadre of American and foreign scientists now have the skills and knowledge to strengthen global research efforts related to emerging and re-emerging microbes and diseases. The AITRP has trained scientists from more than 60 countries, providing a network for the exchange of scientific information about the AIDS pandemic specifically and infectious diseases in general.

In addition, for over two decades, the National Institute of Allergy and Infectious Diseases (NIAID) has supported overseas research programs focused on diseases of public health significance to people living in tropical and subtropical regions, emphasizing parasitic, bacterial and viral infections and also of significance to the developed world. The FIC AITRP, and the NIAID's Division of Microbiology and Infectious Diseases have a mutual interest in this area and are uniquely situated to deal with emerging and re-emerging infectious diseases in a number of ways, for example, by establishing a bridge mechanism between these two global programs.

The NIH is participating with other agencies of the Federal government in an effort by the Committee on International Science, Engineering and Technology (CISET) of the National Science and Technology Committee to address issues related to infectious diseases. The CISET Working Group on Emerging and Re-Emerging Diseases includes a particular focus on surveillance as well as research and infrastructure development.

This group, which includes representatives from FIC and NIAID among others, has noted the importance of international, laboratory-based surveillance for infectious diseases. While such an effort does not come under the purview of any single U.S. agency, there exists in various U.S. government agencies a global network of field stations and expertise that, if coordinated and strengthened, could form the foundation for an effective infectious disease surveillance system.

An inventory of U.S.-supported activities is being developed under CISET that includes laboratories in Africa, Asia and the Americas that are currently maintained by the NIH, Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), Department of Agriculture, U.S. Agency for International Development (USAID), and others. This international network of sentinel outposts, including those supported under the FIC AITRP, could be coordinated to provide U.S. public health agencies with current and accurate information needed to help prevent epidemic disease. Activities include the following:

- CDC-supported field stations;
- DOD-supported field laboratories;
- USAID-supported overseas activities; and
- NIH-supported research and training efforts, such as the International Collaboration in Infectious Disease Research Centers and Tropical Medicine Research Centers of the National Institute of Allergy and Infectious Disease, and the FIC AIDS International Training and Research Program.

Of particular importance in the development of a global surveillance network will be strengthening diagnostic capabilities worldwide and developing collaborations among epidemiological networks, diagnostic laboratories, and laboratory and clinical research institutions. Capacity-building is needed in several areas, including human resource capabilities in epidemiology, clinical medicine, and laboratory research and diagnosis.

In addition to U.S.-supported activities, other relevant efforts include World Health Organization (WHO) collaborating centers. The WHO should serve as a key focal point for coordinating international efforts in surveillance.

ERADICATION OF POLIO WORLDWIDE

Mr. Porter: Is your Center involved with the Rotary effort to eradicate polio worldwide?

Dr. Schambra: Rotary International should be commended for its efforts to assist worldwide efforts to eradicate polio. Through "Polioplus," Rotary has supported the purchase of vaccines, and has applied the considerable organizational skills of its members to strengthen polio vaccination programs where they are needed most, particularly in Bangladesh, Pakistan, India, and Africa. Rotary Club members in Japan are active advocates of support for the eradication of polio in Asia. These collective efforts are integrated with the WHO Polio Eradication Program.

Since these efforts largely constitute health services, the FIC has no direct involvement. However, prior to these events, we were very fortunate to have Dr. Albert Sabin, one of the pioneers in polio research, at the

Fogarty Center for a number of years. Dr. Sabin's discovery of the oral vaccine against poliomyelitis was instrumental in curbing this terrible disease, and during the time at the Center he played a major role in developing the strategy that led to the eradication of polio in the Americas, and which formed the basis for the current effort to eradicate polio worldwide.

In addition, through FIC's participation in the U.S.-Japan Common Agenda, a bilateral program to promote scientific cooperation between the two countries, FIC recently contributed to a major shift in Japanese foreign aid toward support for the elimination of polio in Asia.

NIH SUPPORT OF FOREIGN RESEARCH AND FOREIGN SCIENTISTS

Mr. Porter: Apparently, AIDS vaccines are likely to first be field tested overseas, for example in sites in Africa. Are you involved in what could be the rather delicate work of negotiating agreements to conduct AIDS vaccine trials overseas and in preparing for their implementation?

Dr. Schambra: At present, the NIH is conducting studies to determine the feasibility of eventually conducting vaccine efficacy trials in international sites. Based on the current state of the science, the NIH has made the decision not to proceed with full-scale efficacy trials at this time. When a candidate vaccine is available to be tested in the field, initial trials to test for safety and the ability to elicit an immune response will be conducted in the United States.

Depending upon the progress in the development and initial testing of vaccine candidates, in future the NIH may support international vaccine trials. The relationships established as part of the feasibility studies will form the basis for conducting the vaccine trials. If the NIH were to proceed to conduct such trials, FIC would assist negotiations with foreign governments in its role as NIH liaison with the Department of State (DOS). FIC has served a key role in past negotiations with foreign governments to develop bilateral agreements in biomedical research, including clinical trials to test a candidate vaccine against typhoid fever in Nepal. In addition to clearance by DOS, as well as standard review by an Institutional Review Board for human subjects protections, any trials conducted in foreign countries will also be approved by the government where the trial is conducted. Such trials will also be conducted in close consultation with the WHO.

The primary role of the FIC with respect to vaccine-related research is the development of infrastructure for large-scale vaccine efficacy trials that may proceed in foreign countries. Such infrastructure includes training of scientists in research techniques and technologies, development of laboratory capabilities, and establishment of cohorts for studies. These efforts are conducted in close collaboration with the NIAID to ensure that the infrastructure in place appropriately supports the sites of potential future vaccine trials. These activities not only support future vaccine trials, but other interventions, including strategies to reduce mother to infant transmission of HIV.

Mr. Porter: Can you review for us how much research NIH funds outside the United States and how many foreign-born scientists work in this country, in particular, how many work on the NIH campus?

Dr. Schambra: The NIH awards grants and contracts to foreign investigators to conduct studies that could not be pursued in the U.S alone and are of priority for the American public. These awards are authorized under the provisions of the International Health Research Act of 1960, which acknowledges the special opportunities to further research programs through the use of unusual talents, resources, populations and environmental conditions in other countries. These criteria must be met before a foreign award is made. All foreign awards are reviewed by the NIH peer review process and approved by National Advisory Councils of the awarding institute, after considering if identical studies could be conducted in the United States.

In FY 1994, $33.2 million was expended on foreign grants and cooperative agreements, $17.6 million on foreign contracts, and $27.4 million on foreign components of domestic research grants and contracts. In the aggregate, this represents less than one percent of total NIH extramural expenditures--a percentage that has remained relatively constant since 1974.

The NIH policy of funding foreign investigators on a restricted, highly selective basis positions the agency to capitalize on unique opportunities to advance understanding of disease processes and develop medical solutions. Recent accomplishments under NIH foreign grant support include the discovery of the genes for cystic fibrosis, for a hereditary form of colon cancer, and for Huntington's disease. In addition, a foreign contract to Swedish investigators resulted in an improved vaccine for whooping cough (pertussis).

The average funding level of foreign grants is less than one-half that of domestic awards, in large part because foreign institutions are not eligible for indirect costs. Support for overhead charges such as administrative costs, building maintenance, utilities, new facilities and support personnel are provided by the foreign institution. Foreign awards can also reduce the costs of national programs by providing access to special populations, where research can be conducted in a more cost-effective manner, or through the development of diagnostic and preventive measures which contain health care costs in the United States. For example, international field trials resulted in a recombinant-based hepatitis B vaccine.

At the NIH, foreign scientists hold appointments under the auspices of the Visiting Program, established in 1950 under the Public Service Act. Visiting researchers are supported from 1-5 years, depending on the requirements of the NIH research program. In FY 1994, 3,139 scientists participated in the Visiting Program. This attests to the high international regard for the NIH intramural program.

The NIH Visiting Program has enabled the NIH to bring to its laboratories outstanding scientists in all research disciplines, regardless of nationality. Our investment in this program has contributed significantly to many of the major research advances. In a sampling of the most productive of NIH laboratories, an average of 46 percent of scientific publications were co-authored by visiting researchers. The Visiting Program has contributed to research advances at NIH which include the development of a diagnostic test for HIV and the drug AZT, the most commonly used anti-viral for HIV infection.

Visiting researchers frequently retain close associations with their NIH colleagues when they return home and continue to work in partnership on projects of mutual interest. The Visiting Program in fact has helped to create an international cadre of talented researchers working toward common public health goals.

NIH support for foreign scientists is reciprocated through fellowship programs for U.S. scientists supported by other nations. The FIC administers eleven such programs, supported by the following countries: Germany, Austria, Finland, France, Ireland, Israel, Japan, Norway, Sweden, Switzerland, Taiwan.

The NIH does not possess data on the numbers of foreign-born scientists in the United States. However, the National Science Foundation reports that, in 1991, 46 percent of postdoctoral appointees in the biological sciences were non-U.S. citizens (Foreign Participation in U.S. Academic Science and Engineering: 1991). These scientists hold temporary research and teaching positions at universities and non-profit institutions. No equivalent data exists for permanent employment in the biological sciences.

RE-EMERGING INFECTIOUS DISEASES

Mr. Stokes: To what extent does the re-emergence of infectious diseases that we are experiencing and anticipating here in our country reflect the state of health globally?

Dr. Schambra: In recent years, unexpected epidemics have surfaced that threaten the public health both in the U.S. and in other countries. Examples include Hantavirus, Lyme disease, and Legionnaire's Disease in the U.S. and HIV/AIDS, cholera, plague, and Dengue fever around the world. In some cases, such as Hantavirus, diseases that are endemic to one geographical region (Asia) suddenly emerge in another (southwestern U.S.). While some emerging diseases such as multi-drug resistant tuberculosis, Chagas' disease, and leishmaniasis are related to HIV infection here and abroad, many others are not. These examples demonstrate that, while modern science has made much progress in the ability to prevent and treat infectious disease, they remain a dynamic problem.

As the world population increases and developmental stresses on the environment increase, it may be predicted that additional new infectious diseases will emerge and that diseases that are currently quiescent will become health threats. Changes that could potentially impact on the emergence of disease include: the migration of peoples; urbanization; individual and social behavioral changes; changes in food production and processing; changes in land-use and agricultural practices, including both deforestation and reforestation; breakdown of public health measures; and sanitation problems that may be either chronic or acutely associated with natural disasters or war. While it is thought that changes in the environment or human ecology account for most emerging diseases, such influences are compounded by continued evolution of viruses, bacteria, and parasites, often to more virulent forms, forms that can evade our natural immunity, or forms that are resistant to antibiotics.

As the AIDS epidemic has demonstrated, the prevention of disease is a global issue, and the emergence or re-emergence of infectious diseases in one geographical region has the potential to profoundly impact on the rest of the world. Conditions that favor the emergence of disease in one region, combined with increased international travel, provide the foundation for the emergence of global pandemics. Approaches to addressing the issue of emerging disease can not afford to ignore the global nature of the issue. In a 1992 report, a committee of the Institute of Medicine noted that we can be "confident that new diseases will emerge" and that steps must be taken to prepare for these eventualities. International collaborative research is needed to identify conditions that are conducive to the emergence or reemergence of infectious diseases. In addition, the global capabilities to respond to new health threats must be strengthened.

Mr. Stokes: What major activity is underway at the Center to ensure the appropriate emphasis in this area?

Dr. Schambra: The FIC-sponsored AIDS International Training and Research Program (AITRP) provides a mechanism to address emerging health threats that are related to HIV infection such as tuberculosis. Through grants to U.S. institutions, the AITRP helps to establish a cadre of foreign scientists trained in the epidemiology, diagnosis and treatment of HIV/AIDS and enables the establishment of collaborative relationships between U.S. scientists and scientists in developing countries. Closely coordinated with international HIV-related research of the NIH Institutes, research conducted under the AITRP addresses questions of global importance.

In its long-range plan, FIC has identified as a new initiative the development of a program modeled on the AITRP that would support research and training related to emerging and re-emerging diseases. Such a program would foster cooperative research with regions of the world where new infections are most likely to occur due to population patterns, socioeconomic problems and ecological changes. The program would develop international, multi-disciplinary research partnerships to address the epidemiologic and biologic principles that determine the emergence and re-emergence of microbial diseases and to address the prevention, control, and treatment of these diseases. However, fiscal constraints have thus far precluded initiating this program.

The program would be closely coordinated with NIAID-supported research in this area as well as related efforts by CDC and the World Health Organization. Areas of international research and training that will be addressed under this area of emphasis include:

o ecologic, environmental, and microbial factors affecting disease emergence and development of antibiotic resistance;

o host interactions;

o mechanisms of transmission, establishment of infection, and pathogenesis;

o epidemiology of emerging diseases and relationships with other diseases endemic to the geographical area such as malaria, cholera, sexually transmitted diseases, and HIV;

- development of diagnostic technologies; and
- training in clinical and laboratory diagnosis.

Mr. Stokes: How much is included in the Center's FY 1996 budget request for AIDS, and how does this compare with the funding level for FY 1995 and FY 1994?

Dr. Schambra: The FIC AIDS budget request for FY 1996 is $9,694,000, as compared to funding levels of $9,108,00 for FY 1995 and $8,852,000 for FY 1994.

ENVIRONMENTAL HAZARDS

Mr. Stokes: According to the Justification, the Center is working in collaboration with the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health to further the understanding of the effects of environmental health agents on human health and to develop new interventions for this health problem. What are the major joint environmental research initiatives that are underway and that are planned for FY 1996?

Dr. Schambra: Environmental toxins are increasingly recognized as important factors in the etiology of cancer, respiratory disease, kidney disease, autoimmune disorders, and developmental and behavioral disorders--diseases of interest to nearly all components of the NIH. These hazards are transnational in scope and underscore the importance of international cooperation to identify and validate biological markers for environmentally-induced diseases and to develop interventions to prevent diseases in populations with known toxic exposures, both in the environment and the workplace.

In cooperation with the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (CDC), the FIC will launch an International Training Program in Environmental and Occupational Health. The program will increase global research capacity related to environmental and occupational hazards, including expertise in epidemiology, industrial hygiene, atmospheric chemistry, toxicology, risk assessment, hazardous waste disposal and biomechanics.

The program also will enable NIH- and CDC-supported scientists to establish research and training partnerships in regions of the world which present unique opportunities to study the effects of environmental agents on human health and to develop new interventions. The potential adverse health effects resulting from exposures to environmental chemicals are often first identified in populations of other countries. These include studies on the carcinogenicity of dioxin, the neurotoxic effects of methylmercury and the reproductive toxicity of polychlorinated biphenyls.

Major objectives are as follows:

- o Develop research capacity to identify the biological mechanisms of toxicity, radiation damage and DNA repair through multidisciplinary studies among populations with toxic exposures, and to develop strategies for prevention.
- o Transfer skills and knowledge to enable emerging democracies of the former Soviet sphere and developing nations to assess, mitigate and prevent current and prospective health hazards in the environment and workplace.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Center, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years, explain.

Dr. Schambra: The FIC did not begin to use the Research Project Grant (RPG) mechanism until FY 1994 with the support of two International Cooperative Biodiversity Groups awards. In addition, as part of the FY 1996 budget request, NIH has realigned the RPG mechanism to include small grants (RO3s). Comparable success rates for FIC are as follows: FY 1994 - 27%, FY 1995 estimate - 38%, and FY 1996 estimate - 24%.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Schambra: As previously mentioned, the FIC supports two programs utilizing the research project grant mechanism: the International Cooperative Biodiversity Groups (ICBG) and the Fogarty International Research Collaborative Award (FIRCA). The average cost of these two programs vary significantly and, therefore, are displayed separately in the following table.

AVERAGE AWARD COST

($ in Thousands)

	ICBG	FIRCA
FY 1994	$400	$24
FY 1995	$416	$24
FY 1996	$432	$24

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Schambra: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, the FIC is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. The following information on FY 1994 is provided for those who chose to provide race and gender information versus the "unknown" category. Since there is no way to determine the race and gender of the applicants in the "unknown" category, the data provided may not provide a true representation of the FIC's support of minority researchers, women, or African Americans.

SUCCESS RATES

Asian	Hispanic	Unknown	White	Female
40%	33%	40%	20%	39%

No research project grant applications were received from African American and Native Americans.

The FIC received only one research project grant application from a HBCU, which was not funded. Although not included in the research project grant mechanism, the FIC, however, is supporting 16 HBCUs through the Minority International Research Training Program.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women? To minority researchers? To African American researchers? To HBCUs?

Dr. Schambra: The average cost for minority and women funded research project grants are as follows:

AVERAGE COST

($ in Thousands)

Asian	Hispanic	Unknown	White	Female
$ 21	$ 33	$ 54	$ 50	$ 23

As previously noted, the FIC did not begin to use the Research Project Grant (RPG) mechanism until FY 1994, with the support of two International Cooperative Biodiversity Groups awards. In addition, as part of the FY 1996 budget request, NIH has realigned the RPG mechanism to include small grants (RO3s). Consequently, trend data is not yet available for the Center.

ENVIRONMENTALLY-INDUCED DISEASES

Ms. Lowey: You mention the Center's work on environmentally-induced diseases, particularly present in countries undergoing rapid industrialization. Could you describe for the Committee in greater detail how the Center works with NIEHS and NIOSH--are your efforts duplicative, or does each entity bring something different to the table?

Dr. Schambra: Environmental toxins are increasingly recognized as important factors in the etiology of cancer, respiratory disease, kidney disease, autoimmune disorders, and developmental and behavioral disorders--diseases of interest to nearly all components of the NIH. These hazards are transnational in scope and underscore the importance of international cooperation to identify and validate biological markers for environmentally-induced diseases and to develop interventions to prevent diseases in populations with known toxic exposures, both in the environment and the workplace.

As an outcome of the FIC long-range plan, and mounting global health concerns, the FIC has created an initiative to support collaborations between U.S. and foreign scientists conducting environmental and occupational health research. Given the need for multidisciplinary approaches in these areas, the FIC designed the initiative to include the National Institute of Environmental Health Sciences (NIEHS) and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention.

These agencies have distinct, but complementary missions. The FIC serves as an organizational locus for NIH international activities with extensive experience in launching international programs. It works to advance the NIH mission through international exchanges, fellowships and grants, inter-agency collaboration, and through bilateral and multilateral agreements between countries. NIEHS supports research to define how environmental exposures affect health, and how individuals differ in their susceptibility to these effects. NIOSH conducts research and makes recommendations on workplace safety and health standards.

Each agency makes a critical contribution to the whole. The mechanism of support for this new FIC program is based on a well-tested and successful FIC model for training and research. The international collaborations complement and extend ongoing domestic investments by NIEHS through the Environmental Health Research Centers, and by NIOSH through the Educational Resource Centers and Centers for Agricultural Disease and Injury Research, Education and Prevention.

REPRODUCTIVE HEALTH

Ms. Lowey: You mention your work with NICHD on Population and Health. Could you explain this work to the Subcommittee? How do the scientists for American universities work with scientists in developing nations to "improve reproductive health?"

Dr. Schambra: Following completion of the FIC long-range plan, the FIC and National Institute of Child Health and Human Development (NICHD) discussed the potential role of the NIH in meeting the challenge of sustainable population growth.

As an outcome of these discussions, we have launched an international research and training program on population and health. The intent is to transfer research skills and knowledge to enable developing nations to improve reproductive and neonatal health care, family planning services and demographic capabilities. The program also will assist developing nations to better understand the social and behavioral determinants of population change, in support of policies that are responsive to cultural needs.

International research and training grants will be awarded competitively to U.S. universities with population research and training programs supported by NIH. These funds will enable American faculty to enter into partnerships with scientists and institutions in developing nations. Emphasis will be placed on the training of scientists from developing nations in the biomedical, behavioral and demographic sciences, and cooperative studies conducted in-country on reproductive and maternal health priorities.

The program is based on a successful international program model established by FIC to combat HIV/AIDS. The FIC AIDS International Training and Research Program has trained scientists and health professionals from over 50 developing nations in laboratory and field study skills to combat the HIV/AIDS pandemic. It has helped develop a cadre of scientists to launch national prevention programs and participate in future international vaccine trials and other interventions.

The Request for Applications for this program was issued on November 18, 1994, with an applications receipt date of April 20, 1995. After standard peer review, funding decisions will be made by September 30, 1995. It is anticipated that six to seven awards will be made, with individual awards of up to $150,000 direct costs for the first year.

A component of this program will be the formation of a network of investigators conducting international research in population and health. This network will provide a mechanism for coordination and information-sharing among investigators and with the population activities of the

World Health Organization, as well as activities resulting from the U.N. International Conference on Population and Development, which convened in Cairo in September of 1994.

MIDDLE-EAST AND ENVIRONMENTAL ISSUES

Ms. Lowey: I found your mention of the cooperative program assessing environmental risks of pesticides in the Middle East very interesting. Would you elaborate, and tell the Committee how you see this work as "supporting" the peace process in the Middle East?

Dr. Schambra: Today's Middle East peace negotiations are being carried out within the structure of the Madrid Framework which was established in 1991. Within the Framework, a series of ongoing multilateral discussions and deliberations are focusing upon key issues that concern the entire Middle East--environment, water, arms control, refugees and economic development--with a working group convened for each topic.

In conjunction with the National Institute of Environmental Health Sciences (NIEHS), the FIC was instrumental in developing a proposal to examine the health effects of pesticide use in the Middle East. Participant nations to the peace process have expressed concern and frustration that dramatic environmental impacts of population, agricultural, technological and industrial changes have been underrecognized by governments and the general public.

Working with the Department of State, the Environmental Protection Agency and the Department of Agriculture, FIC and NIEHS developed a long-term project to identify the adverse health effects of agricultural chemical use in the region and to craft strategies to reduce their impact. In December 1994, FIC participated in a workshop held in Cairo, Egypt to prepare future steps in gathering usage data and promoting technical cooperation. Since the workshop, NIEHS has been contributing its scientific expertise for pilot projects in the region.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

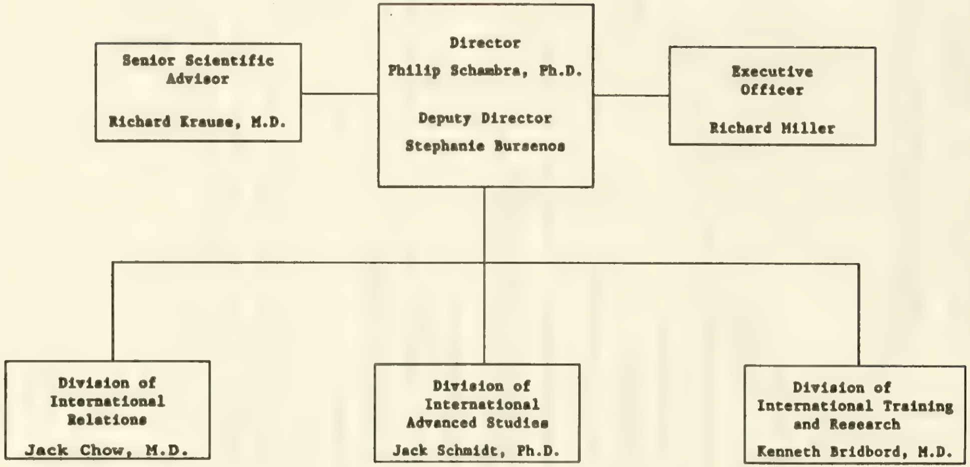
FY 1996 Budget — Page No.

Organization chart 36
Appropriation language 37
Amounts available for obligation 39
Budget mechanism table 40
Summary of changes 41
Budget authority by object 43
Administrative costs 45
Significant items in House and Senate Appropriations Committee reports 46
Authorizing legislation 48
Appropriation history 49
Budget authority by activity 50

Justification:

A. General statement 51
B. International research activities 58
C. Research management and support 60
D. Detail of full-time equivalent employment (FTE) 62
E. Detail of end-of-year employment 63

NATIONAL INSTITUTES OF HEALTH
John E. Fogarty International Center
Organizational Chart



NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

For carrying out Sections 301, 307 and title IV of the Public Health Service Act with respect to the John E. Fogarty International Center, [$14,697,000] *$15,267,000*.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation	$21,677,000	$14,697,000	$15,267,000
Section 205 Procurement reduction		-12,000	
Section 513 S&E reduction		-18,000	
Subtotal, Adjusted Appropriation	21,677,000	14,667,000	15,267,000
Comparative transfer to: Office of AIDS Research, NIH for NIH activities	-8,852,000		
Subtotal, adjusted budget authority	12,825,000	14,667,000	15,267,000
Unobligated balance, lapsing	-15,000		
Total, obligations	12,810,000	14,667,000	15,267,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994 - $8,514,000; FY 1995 - $10,878,000; and FY 1996 - $11,219,000.

Also excludes funding for HIV activities: FY 1995--$9,108,000; FY 1996--$9,694,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting..............	60	$1,492,000	55	$2,170,000	81	$2,885,000
Admin. supplementals......	(4)	84,000	(6)	152,000	--	---
Competing:						
Renewal.................	2	44,000	13	300,000	6	138,000
New.....................	23	1,278,000	45	1,035,000	40	917,000
Subtotal, competing...	25	1,322,000	58	1,335,000	46	1,055,000
Subtotal, res. proj.....	85	2,898,000	113	3,657,000	127	3,940,000
Other Research						
Other research related....	113	3,516,000	118	4,492,000	118	4,712,000
Subtotal, other research	113	3,516,000	118	4,492,000	118	4,712,000
Total, research grants......	198	6,414,000	231	8,149,000	245	8,652,000
	FTEs		FTEs		FTEs	
Research Management and Support....................	68	6,411,000	76	6,518,000	75	6,615,000
Total....................	68	12,825,000	76	14,667,000	75	15,267,000

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Summary of Changes

1995 Estimated budget authority	$14,667,000
1996 Estimated budget authority	15,267,000
Net change	+600,000

	Current 1995 Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Research Management and Support				
a. Within grade increase		$3,683,000		+$49,000
b. One more day of pay		3,683,000		+14,000
c. Annualization of January 1995 Locality Pay increase		3,683,000		+14,000
d. January 1996 pay increase		3,683,000		+61,000
e. Payment for centrally furnished services		892,000		+37,000
f. Service and supply fund increase		221,000		+20,000
g. Increased cost of supplies, materials, and other mandatory program expenses		1,608,000		+41,000
h. DHHS Working Capital Fund increase		66,000		-3,000
i. Increase for FTS		45,000		+9,000
Subtotal, built-in				+242,000

Summary of Changes--continued

B. Program:	No.	Amount	No.	Amount
1. Research Project Grants				
a. Noncompeting...............	55	2,170,000	+26	+715,000
b. Admin supplements..........	(6)	152,000	-(6)	-152,000
c. Competing..................	58	1,335,000	-12	-280,000
Total.................		3,505,000	+14	+283,000
2. Other Research				
a. Other research related.....	118	4,492,000	---	+220,000
	(FTEs)		(FTEs)	
3. Research management and support................	76	6,518,000	-1	-145,000
Subtotal, program..............				+358,000
Total changes..............				+600,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	76	75	-1
Full-time equivalent of overtime and holiday hours.................	1	1	---
Average ES Salary.....................	$111,839	$113,685	+$1,846
Average GM/GS grade...................	9.7	9.7	---
Average GM/GS salary..................	$35,879	$36,471	+$592
Average salary, grades established by act of July 1, 1944 (42 USC 207).	---	---	---
Average salary of ungraded positions..	$52,433	$53,298	+$865
Personnel compensation:			
Full-time permanent.................	$2,691,000	$2,771,000	+$80,000
Other than full-time permanent......	205,000	208,000	+3,000
Other personnel compensation........	94,000	96,000	+2,000
Special personnel service payments..	51,000	52,000	+1,000
Subtotal personnel compensation...	3,041,000	3,127,000	+86,000
Personnel benefits....................	639,000	656,000	+17,000
Benefits for former personnel.........	3,000	3,000	---
Travel and transportation of persons..	95,000	95,000	---

44

	1995 Appropriation	1996 Estimate	Increase or Decrease
Transportation of things.............	12,000	12,000	---
Rent, communications and utilities....	290,000	290,000	---
Printing and reproduction............	47,000	47,000	---
Other services:			
Consulting services................	35,000	35,000	---
Other Services.....................	565,000	563,000	-2,000
Purchases from Govt. Accts..........	1,669,000	1,667,000	-2,000
Operation of GOCO's................	---	---	---
R&D Contracts......................	---	---	---
Supplies amd materials...............	62,000	60,000	-2,000
Equipment............................	60,000	60,000	---
Grants, subsidies, and contributions..	8,149,000	8,652,000	+503,000
Total.........................	14,667,000	15,267,000	+600,000

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for the Advanced Study in the Health Sciences

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1).............	$2,691,000	$2,771,000	+$80,000
Other than Full-Time Permanent (11.3)...	205,000	208,000	+3,000
Other Personnel Compensation (11.5).....	94,000	96,000	+2,000
Special Personnel Services Payments (11.8)	51,000	52,000	+1,000
Total Personnel Compensation (11.9)...	3,041,000	3,127,000	+86,000
Civilian Personnel Benefits (12.0)......	639,000	656,000	+17,000
Benefits for former personnel (13.0)....	3,000	3,000	---
Travel (21.0).........................	95,000	95,000	---
Transportation of Things (22.0).........	12,000	12,000	---
Rental Payments to Others (23.2)........	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3)...........	290,000	290,000	---
Printing and Reproduction (24.0)........	47,000	47,000	---
Consulting Services (25.1).............	35,000	35,000	---
Other Services (25.2)..................	565,000	563,000	---
Purchases from Govt. Accts. (25.3)......	1,551,000	1,549,000	-2,000
Operation of GOCO's (25.4)..............	---	---	---
Supplies and Materials (26.0)...........	62,000	60,000	-2,000
	6,340,000	6,437,000	+97,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Significant Items in House and Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
1995 House Report Environmental Health 1. The House in its report 103-553, page 65, stated, "The Committee encourages FIC to consider commencing fellowships in the area of occupational and environmental health, if it would be consistent with the Center's strategic plan. This effort would provide for an exchange of information in research and related environmental and occupational concerns."	1. The FIC's International Training and Research Program on the Environment and Health, initiated in FY 1995, will help to increase global capacity to identify and address health risks related to environmental change and degradation. This program, in collaboration with the National Institute of Environmental Health Sciences of the NIH and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, will train scientists to deal effectively with environmental and occupational health problems through epidemiologic research, environmental monitoring, engineering control and prevention research. The FIC will fund two awards in FY 1995.

Item	Action Taken or To Be Taken
1995 Senate Report Environmental Health 1. The Senate in its report 103-318, page 108, stated, "The Committee encourages FIC to consider commencing fellowships in the area of occupational and environmental health, if it would be consistent with the Center's strategic plan. This effort	1. The FIC's International Training and Research Program on the Environment and Health, initiated in FY 1995, will help to increase global capacity to identify and address health risks related to environmental change and degradation. This program, in collaboration with the National Institute of Environmental Health Sciences of the NIH and the

would provide for an exchange of information on research and related environmental and occupational concerns."

National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, will train scientists to deal effectively with environmental and occupational health problems through epidemiologic research, environmental monitoring, engineering control and prevention research. The FIC will fund two awards in FY 1995.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation.......	Section 301	42§241	Indefinite	$14,667,000	Indefinite	$15,267,000
International Cooperation.........	Section 307	42§242e	Indefinite		Indefinite	
Fogarty International Center.............	Title IV, Part E	42§287b	Indefinite		Indefinite	
Total Budget Authority				14,667,000		15,267,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$11,305,000	$11,443,000	$11,420,000	$11,420,000
1988	11,166,000	12,128,000 2/	11,166,000	15,651,000
1989	11,338,000	16,074,000	16,474,000	15,848,000
1990	10,622,000 3/	15,579,000	15,532,000	15,516,000
1991	16,355,000	18,682,000	17,436,000	17,519,000 4/
1992	19,922,000	19,922,000	19,922,000	19,593,000 5/
1993	20,002,000	19,932,000	19,609,000	19,733,000 6/
1994	19,988,000	22,240,000	19,988,000	21,677,000
1995 7/	13,733,000	15,181,000	13,197,000	14,667,000 8/
1996 7/	15,267,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.
3/ Does not include HIV-related funds, which were requested in a consolidated amount under the Office of the Assistant Secretary for Health.
4/ Reflects enacted administrative reductions of $540,000.
5/ Reflects enacted administrative reductions of $313,000 and rescission of $16,000.
6/ Reflects enacted administrative reductions of $268,620.
7/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.
8/ Excludes enacted administrative reductions of $12,000 and $18,000.

John E. Fogarty International Center for Advanced Study in the Health Sciences

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
International research activities	---	$7,253	--	$7,440	--	$6,414	--	$8,149	--	$8,652	---	+$503
Research management and support	72	6,728	75	6,578	68	6,396	76	6,518	75	6,615	-1	+97
Total, obligations	72	13,981	75	14,018	68	12,810	76	14,667	75	15,267	-1	+600
Unobligated balance lapsing		19		13		15		---		---		---
Total, budget authority	72	14,000	75	14,031	68	12,825	76	14,667	75	15,267	-1	+600

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
68	$12,825,000	76	$14,667,000	75	$15,267,000	-1	+$600,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the Fogarty International Center (FIC). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The wealth of a country derives from the health of its people. For the sick and diseased, the restoration of health is the overriding concern of their lives. For the healthy, the threat of illness is a constant, though less acute, concern. The Fogarty International Center (FIC) plays a significant role in improving the health of people worldwide through international cooperation in the biomedical sciences.

The FIC has completed a major planning effort this past year entitled "International Frontiers in Biomedical Research: A Long-Range Plan for the Fogarty International Center." As a result of this effort, the FIC has adopted the following four goals:

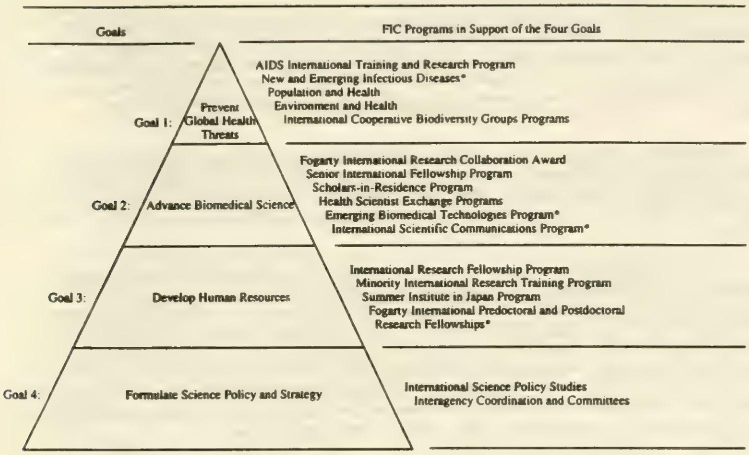
Goal 1: Mobilize International Research Efforts Against Global Health Threats.

Goal 2: Advance Science Through International Cooperation

Goal 3: Develop Human Resources to Meet Global Research Challenges

Goal 4: Provide Leadership in International Science Policy and Research Strategies

FIC's goals, and programs and activities in support of these goals, are depicted in the following chart. Future initiatives are identified by an asterisk (*).


Goals
FIC Programs in Support of the Four Goals
Goal 1:
Prevent Global Health Threats
AIDS International Training and Research Program
New and Emerging Infectious Diseases*
Population and Health
Environment and Health
International Cooperative Biodiversity Groups Programs
Goal 2:
Advance Biomedical Science
Fogarty International Research Collaboration Award
Senior International Fellowship Program
Scholars-in-Residence Program
Health Scientist Exchange Programs
Emerging Biomedical Technologies Program*
International Scientific Communications Program*
Goal 3:
Develop Human Resources
International Research Fellowship Program
Minority International Research Training Program
Summer Institute in Japan Program
Fogarty International Predoctoral and Postdoctoral Research Fellowships*
Goal 4:
Formulate Science Policy and Strategy
International Science Policy Studies
Interagency Coordination and Committees

Goal 1:
Mobilize International Research Efforts Against Global Health Threats

A key role for the Fogarty International Center is to protect American citizens from global health threats that have their origin in: population growth no longer sustainable by the world's resources; industrial and agricultural pollution of atmosphere, land, rivers, lakes and oceans; migration of refugees; the growth of megacities with the morass of congestion, poverty, and disruption of social and health services; and geographic and ecological disasters. AIDS is but the most recent example of a new disease that has spread worldwide from a focus in Africa where humans encroached on native habitats. Industrial pollutants in Eastern Europe have fostered high levels of lung diseases and cancer. The Chernobyl disaster spread toxic radiation waste to neighboring countries from Ukraine. Bacterial diseases have been spread in the U.S. by the distribution of meat and poultry products from mass production processing plants. New microbes have eluded the water purification systems of large American metropolitan areas.

The Fogarty International Center has developed research and training programs to mobilize global scientific efforts to meet these threats to the health of the American people.

Population and Health--Although the world population growth rate peaked at 2.3 percent and began to decline in the late 1970's, the age structure of the present population will result in an increase of the world population to 8.5 billion in the next thirty-five years. This trend has significant ramifications for global health in developing nations. High birth rates will increase industrialization and consumer consumption that surpasses sustainable economic development. Consequences may include: greater pollution and overburdened sanitation systems; the emergence and spread of infectious diseases; over-exploitation of land; destruction of natural ecosystems;

unemployment; and inadequate access to health care and education. Solutions to these problems require new knowledge based on multidisciplinary research. For this reason the FIC initiated an international training and research program in those sciences concerned with health and population for scientists in developing countries. The purpose is to identify the technological and social adaptations that are needed to meet the challenge of population growth.

Environment and Health--Insidious health risks are presented by rising concentrations of industrial and chemical pollutants. Environmental toxins are increasingly recognized as important factors in the origins of cancer, respiratory disease, kidney disease, and autoimmune and developmental disorders.

As we look toward the future, it is clear that environmental and worker safety and health research are becoming more and more dependent upon international collaboration. Environmental threats resulting from industrial accidents, including radiation exposure, and the health impact of global climate change due to ozone depletion and increasing levels of atmospheric CO_2, are hazards that are transnational in scope. They underscore the importance of international cooperation to identify and validate biological markers for environmentally-induced diseases and to develop interventions to prevent diseases in populations with known toxic exposures.

The FIC's International Training and Research Program on the Environment and Health will help to increase global capacity to identify and address health risks related to environmental change and degradation. This program, in collaboration with the National Institute of Environmental Health Sciences of NIH, and the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, will train scientists to deal effectively with environmental and occupational health problems through epidemiologic research, environmental monitoring, engineering control and prevention research.

Biodiversity--Biological diversity refers to the rich variety of the earth's fauna and flora. NIH-supported researchers are working in many regions of the world to discover and develop medical products from nature, conducting research to benefit health, enhance conservation, and promote economic development.

About 40 percent of modern pharmaceuticals, ranging from penicillin to taxol, originated in nature. These include treatments for cancer, glaucoma, malaria, Parkinson's disease, high blood pressure, inflammatory disorders, and infections, to name a few. Yet less than 5 percent of the world's plant and marine species have been screened for potential therapeutic benefits.

The FIC administers and supports the International Cooperative Biodiversity Groups Program, an interagency effort co-supported by the U.S. Agency for International Development; the National Science Foundation; and the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health and the National Heart, Lung, and Blood Institute of NIH. This Program supports projects on biodiversity conservation and the promotion of sustainable economic activity through drug discovery from natural products. Scientists and institutions in the United States, with their counterparts in Argentina, Cameroon, Chile, Costa Rica, Mexico and Suriname, are seeking new bioactive natural products from plant and marine extracts and microorganisms. Efforts are also directed to preserving the rich natural diversity of rain forests and oceans.

Goal 2:
Advance Science Through International Cooperation

International cooperation fosters discovery through the exchange of innovative concepts and new research technologies, and the access to unique populations and environments. Both new and long-standing FIC programs support these efforts.

As an example, the Fogarty International Research Collaboration Award (FIRCA) was established in FY 1992 to support and enhance collaborative research opportunities between American scientists and scientists in Latin America and Eastern Europe. The program will be expanded in FY 1996 to include the regions of Africa, Asia, the Middle East, and the Pacific Ocean Islands. This program promotes broad-based international cooperation on selected global priorities and forges new U.S. scientific ties to regions of the world that possess unexplored scientific opportunities due to past isolation.

The Health Scientist Exchange Program (HSEP) was established to promote contacts and cooperation in the health sciences, and has supported areas of research that include Alzheimer's disease, pulmonary diseases, neuroscience, and osteoporosis. Created in the 1950's to encourage and enhance scientific collaborative efforts with scientists in the U.S. and abroad, this program promoted scientific alliances with the Warsaw Pact nations. Now that these contacts are well-established the FIC will initiate exchange programs only in those countries where scientific contact must be strengthened.

As part of the NIH initiative on Brain and Brain Disorders, the FIC will expand its international research efforts in the neurosciences. Research on the causes of Alzheimer's disease and other neurodegenerative conditions of public health priority will include population-based studies on genetic inheritance patterns and environmental exposures, such as toxins and infectious agents. International studies have already resulted in the discovery of genes associated with Huntington's chorea and neurofibromatosis.

Goal 3:
Develop Human Resources to Meet Global Research Challenges

Future scientists must be prepared to work in a global environment in order to access international sources of scientific and technical information. The FIC plays a significant role in preparing our future scientific leaders to excel in an international arena. Two examples of developing human resources, in addition to supporting scientific research, follow.

The International Research Fellowship (IRF) Program is the most longstanding of FIC programs, predating the establishment of the Center. Over its 35-year history, the IRF Program has contributed to the development of a global research capacity in the biomedical sciences and has proven to be an effective means of enabling U.S. universities to benefit from an international talent pool of foreign educated researchers. One of the conclusions of the FIC's recently completed long-range plan was to recognize the increasing need to provide research and training opportunities for scientists from developing nations. This resulted in a redirection of the IRF Program by shifting the geographic emphasis from developed to developing nations and emerging democracies. This new emphasis expands linkages in regions of the world that are underrepresented in global health research efforts and that are key to the management of HIV/AIDS and emerging infectious diseases, environmental health, population and other transnational challenges.

In cooperation with NIH's Office of Research on Minority Health, the FIC established a Minority International Research Training (MIRT) Program to provide opportunities for undergraduate and graduate students underrepresented in the scientific professions to study abroad at centers of academic excellence. Minority faculty members are also supported to conduct independent biomedical studies at foreign institutions and to serve as mentors to American minority students abroad. In addition to providing unique international training opportunities, the program supports a broad array of research including studies in infectious diseases, gerontology, mental disorders, the neurosciences, and molecular and cellular neuroimmunology.

Goal 4:

Provide Leadership in International Science Policy and Research Strategies

The FIC plays an instrumental role in international policy analysis and formulation at the NIH, U.S. Public Health Service, Departmental and interagency levels. At the multilateral level, the FIC represents the NIH in policy fora convened by the World Health Organization, the Pan American Health Organization, the European Medical Research Councils and the Organization for Economic Cooperation and Development.

As an example, the FIC developed a proposal to establish a Council on Science and Technology in the Americas (COSTA) which would serve as a mechanism for ongoing dialogue among the science and technology ministers of the Western Hemisphere. The ministers would discuss Science and Technology issues relevant to interAmerican interests. This proposal was recently adopted by the Heads of State attending the Summit of the Americas.

The FIC was invited to participate in the Middle East Peace Process. To this end, the FIC recently convened a meeting to discuss opportunities for biomedical cooperation with Palestinian health scientists. Attendees included Dr. Fathi Arafat, head of the Palestine Red Crescent Society, as well as health authorities from the Gaza and the West Bank, and representatives of other countries in the region. Research opportunities discussed included infectious diseases such as acute respiratory infections, hepatitis, and brucellosis and chronic diseases such as cardiopulmonary disease, cancer, and diabetes, as well as enhancement of research capacity through further training, infrastructure development, and joint collaborations. One immediate outcome of the conference was an agreement to accept young Palestinian scientists for training as Fogarty International Research Fellows. In addition, FIC staff worked with the National Institute of Environmental Health Sciences to develop a joint proposal to examine the health effects of pesticides in the Middle East which was discussed and accepted at a workshop sponsored by the Middle East Environmental Working Group.

The President's appropriation request of $15,267,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the FIC during the last five years has been as follows:

Year	Amount	FTE's
FY 1991	$12,168,000	68
FY 1992	14,000,000	72
FY 1993	14,031,000	75
FY 1994	12,825,000	68
FY 1995	14,667,000	76

Purpose and Method of Operation

The FIC carries out the research components of its four strategic goals through a number of international fellowship and award programs that provide research opportunities in a wide range of biomedical research areas.

FIC also funds several scientific programs and services in support of the NIH intramural research programs through its Research and Management Support (RMS) activity. These programs include the Health Scientist Exchange Programs, the U.S.-Japan Summer Institute Program, the Human Frontier Science Program, and administrative support for the NIH Visiting Program.

Overall Budget Policy

The FY 1996 budget request for the FIC is $15,267,000, an increase of $600,000 over the comparable FY 1995 level of $14,667,000. The request includes 75 FTEs, as compared to 76 at the FY 1995 level.

A total of $3,940,000 is requested in Research Project Grants, an increase of $283,000 over the comparable FY 1995 level of $3,657,000. This increase will be used to fund additional research projects in the Fogarty International Research Collaboration Awards Program.

A total of $4,712,000 is requested in Other Research, reflecting an increase of $220,000 over the comparable FY 1995 level of $4,492,000. This increase will be used to fund additional research projects in the FIC's Environment and Health Program and Senior International Fellowship Program.

A total of $6,615,000 will be available in the Research Management and Support mechanism, which reflects an increase of $97,000 over the comparable FY 1995 level of $6,518,000.

NATIONAL INSTITUTES OF HEALTH
Fogarty International Center

Distribution of Funds by Program Goals
(DOLLARS IN THOUSANDS)

	FY 1994		FY 1995		FY 1996	
	No.	Amount	No.	Amount	No.	Amount
MOBILIZE INT'L. RESEARCH EFFORTS AGAINST GLOBAL HEALTH THREATS	**2**	**900**	**17**	**2,288**	**18**	**2,448**
Biodiversity						
International Cooperative Biodiversity Groups Awards	2	900	2	936	2	936
Small Grants	0	0	8	320	8	320
Subtotal	2	900	10	1,256	10	1,256
Environment and Health	0	0	2	200	3	360
Population and Health	0	0	5	832	5	832
ADVANCE SCIENCE THROUGH INTERNATIONAL COOPERATION	**123**	**4,149**	**160**	**4,889**	**173**	**5,235**
Fogarty International Research Collaboration Awards						
Noncompeting	60	1,478	53	1,234	71	1,629
Competing	23	521	50	1,167	46	1,055
Subtotal	83	1,999	103	2,401	117	2,684
Senior International Fellowships						
Noncompeting	16	220	7	106	19	336
Competing	18	440	39	935	29	765
Subtotal	34	660	46	1,041	48	1,101
Scholars-in-Residence						
Noncompeting/Supplements	(15)	382	(11)	270	(15)	375
Competing	6	218	11	395	8	290
Subtotal	6	600	11	665	8	665
Health Scientist Exchange Programs		242		110		110
Conferences and Workshops		148		172		175
Human Frontier Science Program		500		500		500
DEVELOP HUMAN RESOURCES TO MEET GLOBAL RESEARCH CHALLENGES	**73**	**2,313**	**54**	**1,814**	**54**	**1,814**
International Research Fellowships						
Noncompeting	36	1,129	36	1,207	18	558
Competing	34	1,083	18	547	36	1,196
Subtotal	70	2,212	54	1,754	54	1,754
Environmental Fellowships	3	41		0		0
Japan Summer Institute		60		60		60
PROVIDE LEADERSHIP IN INT'L SCIENCE POLICY AND RESEARCH STRATEGIES		**5,448**		**5,676**		**5,781**
FIC Services to NIH Science Programs		1,885		1,934		1,959
FIC Program Administration		3,563		3,742		3,822
TOTAL	**198**	**12,810**	**231**	**14,667**	**245**	**15,278**

John E. Fogarty International Center
for Advanced Study in the Health Sciences

International Research Activities

Authorizing Legislation - Sections 301 and 307 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$6,414,000	$8,149,000	$8,652,000	+$503,000

The FIC supports extramural research and research training through a number of long-standing programs as well as new programs on specific global health threats. Long-standing programs, such as the International Research Fellowship, the Senior International Fellowship and the Scholars-in-Residence programs, continue to strengthen international research efforts by supporting American scientists abroad and foreign scientists in the U.S. The Fogarty International Research Collaboration Award program is a small grant program established in FY 1992 to facilitate collaboration between American scientists and researchers from Latin American and Eastern Europe, and is now being extended to include collaboration with scientists from the regions of Africa, Asia, the Middle East, and the Pacific Ocean Islands. The multi-agency International Cooperative Biodiversity Group program was established in FY 1993 to identify new therapeutic agents through the analysis of plants and organisms from natural ecosystems and traditional medicines, and to promote strategies to protect threatened biodiversity.

Two new programs implemented in FY 1995 to address specific global heath threats identified in the FIC long-range plan are the Environment and Occupational Health and the Population and Health initiatives. Together, these programs help to advance our understanding of preventing and controlling diseases.

The Minority International Research and Training program, established in FY 1993 in conjunction with the NIH Office of Research on Minority Health, will continue to provide international research training opportunities for underrepresented minorities in FY 1996.

Funding for the Fogarty International Research Activities during the last five years has been as follows:

Year	Amount
FY 1991	$5,694,000
FY 1992	7,253,000
FY 1993	7,440,000
FY 1994	6,414,000
FY 1995	8,149,000

Rationale for the Budget Request

Within the FY 1996 extramural request, funds will provide support for the FIC's International Research Activities in the amount of $8,652,000, an increase of $503,000. The increase consists of $283,000 in Research Project Grants for the Fogarty International Research Collaboration Awards Program and $220,000 in Other Research Grants which consists of an increase of $60,000 for the Senior International Research Fellowships Program and $160,000 for the Environment and Health Program. The total number of awards for FY 1996 is 245, an increase of 14 awards from the FY 1995 estimate of 231.

The following research examples are representative of projects that will continue to be funded by the International Research Activities Programs.

American and Slovakian scientists have conducted collaborative research on the bovine leukemia virus, a close relative of the HIV/AIDS virus. They have identified one of the genes that is involved in the virus infection of cells. Such information is needed to develop drugs and vaccines for the HIV/AIDS virus as well as other virus infections.

The energy of every living cell in the body stems from the combustion of foodstuffs. The metabolic processes that yield energy are diverse and complex. In health, there is an harmonious interplay of these processes. In disease, the rhythm is broken. For example, in normal conditions an enzyme called ATP synthase induces the formation of a high energy substance, adenosine triphosphate (ATP), which contains the energy required for the combustion of foodstuffs, cell movement, transport of nutrients and protein synthesis. A FIC Scholar from the United States has demonstrated that these cell "energetics" are markedly altered in certain diseases such as cancer and cystic fibrosis. The objective of this research is to develop new treatments for these diseases such as drugs that will restore the normal patterns of energy metabolism.

The most dangerous tumors are those that grow and invade locally and spread to other regions of the body, a process termed metastasis. American investigators working with scientists in Hungary have identified several biochemical steps that influence the processes of invasion and metastasis. For example, metabolic products of an enzyme termed 12 lipoxygenase (12 Lox) activates three key events of the invasion process. This suggests that 12 Lox is a target for new antimetastatic drugs.

Influenza continues to be a worldwide public health threat. Although the current vaccine is effective in preventing illness, the virus can elude the immunity induced by the vaccine. This occurs when a new flu virus emerges as the result of genetic changes. Such new flu viruses were the cause of the pandemics of 1957 and 1968. For this reason it is important to detect a new flu virus as soon as it occurs and employ it in the formulation of the flu vaccine. A FIC Scholar from the United States in collaboration with scientists at the Food and Drug Administration's Center for Biologics, Evaluation and Research has succeeded in developing a system for analyzing the nature and the extent of the genetic changes in recent influenza virus isolated from the U.S. and elsewhere in the world. The addition of new components to improve the flu vaccine depends on this effort.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Research Management and Support

Authorizing Legislation - Sections 301 and 307 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
68	$6,411,000	76	$6,518,000	75	$6,615,000	-1	+$97,000

A number of distinctive programs are funded through the Research Management and Support (RMS) mechanism, providing resources to support several FIC science programs, as well as services to NIH international science programs. The Health Scientist Exchange Programs, the Human Frontier Science Program and the U.S.-Japan Summer Institute Program are all supported within the RMS mechanism, as well as the International Coordination and Liaison Program and scientific conferences and workshops.

RMS funds also support the FIC International Services and Communications Program which administers the NIH Visiting Program through which foreign postdoctoral scientists and senior foreign scientists conduct research in NIH laboratories in collaboration with their American colleagues.

These endeavors further contribute to international research collaboration by promoting contacts and cooperation between health professionals and biomedical scientists in the U.S. and participating countries. In addition to FIC program activities, RMS funds support all FIC staff and provide for the overall scientific management operations and administrative requirements of the Center.

Funding for the research management and support activity during the last 5 years has been as follows:

Year	Amount	FTE's
FY 1991	$6,474,000	68
FY 1992	6,747,000	72
FY 1993	6,591,000	75
FY 1994	6,411,000	68
FY 1995	6,518,000	76

Rationale for the Budget Request

The FY 1996 budget request for RMS is $6,615,000, which represents an increase of $97,000 from the FY 1996 appropriation. Core program activities are covered in the RMS section along with administrative and program operations costs. The following examples are illustrative of some of the activities that are funded through this mechanism.

Science Programs--Through the Health Scientist Exchange Programs, the FIC supported activities that included research and research training in nuclear medicine, biomedical engineering, hepatitis, hematology, non-Hodgkins lymphoma, and pregnancy-induced hypertension.

The Fogarty Scholars-in-Residence organized and hosted international conferences on domain organization in biological membranes, biological mechanisms and clinical applications of transforming growth factors-ß, the contributions of biomedical engineering to biology and medicine, and programmed cell death.

Policy Development Activities--The FIC's efforts in this area not only impact on the NIH but on other U.S. interests as well. The following types of policy development activities and services will be continued in FY 1996.

FIC staff were instrumental in working with staff of the Mexican National Council for Science and Technology (CONACYT) and bringing to fruition final arrangements for the signing of an agreement between the NIH and CONACYT. Dr. Harold Varmus, NIH Director, and Dr. Fausto Alzate, Director General of the Mexican Council for Science and Technology, signed the agreement on October 17, 1994 to establish a U.S.-Mexico Cooperative Biomedical and Biobehavioral Research Program, which will provide opportunities for Mexican scientists to conduct research and receive advanced research training at the NIH. The FIC is undertaking a number of activities in support of this agreement, including a workshop on addictions research.

The FIC's involvement in the development and implementation of the U.S.-Japan Common Agenda contributed to Japan's decision to devote additional resources for international health activities, including research.

Program Services--The International Services and Communications Program provides overall administrative and technical support for the NIH Visiting Foreign Scientist Program. The FIC has arranged for the participation of over 3,100 foreign scientists in the intramural laboratories of the NIH institutes and other PHS agencies located on the NIH campus, providing visa, immigration, and other administrative support and advice for the foreign scientists. In addition to the normal program operative procedures, FIC staff participated in discussions on important immigration policy issues relating to the NIH on the Exchange Visitor Program, and the most recent changes and interpretations of immigration law and policy, including the resolution of several NIH concerns on immigration procedures that affect the NIH directly.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director.......	21	22	22
Scholars-in-Residence Branch....................	4	5	5
International Services and Communications Branch......	18	20	19
International Studies Branch....................	5	6	6
International Research and Awards Branch.............	8	9	9
International Coordination and Liaison Branch.........	12	14	14
Total FIC.................	68	76	75

Average GS/GM Grade	
1991..	11.15
1992..	9.00
1993..	9.60
1994..	9.79
1995..	9.74
1996..	9.71

NOTE: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for the Advanced Study in the Health Sciences

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-4	1	1	1
Subtotal	1	1	1
Total - ES Salary	$107,300	$111,839	$113,685
GS/GM-15	10	8	8
GS/GM-14	7	9	9
GS/GM-13	5	6	6
GS-12	7	9	8
GS-11	2	2	2
GS-10	2	2	2
GS-9	6	9	9
GS-8	5	5	5
GS-7	8	9	9
GS-6	8	8	8
GS-5	2	3	3
GS-4	3	3	3
GS-3	2	2	2
GS-2	0	0	0
GS-1	1	1	1
Subtotal	68	76	75
Ungraded	1	1	1
Total permanent positions	69	77	76
Total positions, end of year	70	78	77
Total full-time equivalent (FTE) employment, end of year	68	76	75
Average ES level	4.0	4.0	4.0
Average ES salary	$107,300	$111,839	$113,685
Average GS/GM grade	9.7	9.7	9.7
Average GS/GM salary	$34,755	$35,879	$36,471

WEDNESDAY, MARCH 22, 1995.

NATIONAL INSTITUTE OF MENTAL HEALTH

WITNESSES

DR. REX WILLIAM COWDRY, ACTING DIRECTOR
WILLIAM T. FITZSIMMONS, EXECUTIVE OFFICER
RICHARD PINE, BUDGET OFFICER
DR. RUTH L. KIRSCHSTEIN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM R. BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. The subcommittee will come to order.

We continue this afternoon our hearings with the National Institute of Health. We will begin with the National Institute of Mental Health, and we're very pleased to welcome Dr. Rex Cowdry, the Acting Director. Dr. Cowdry, would you introduce the people with you, and please proceed?

Dr. COWDRY. I'd be pleased to, Mr. Porter, it's a pleasure to be here before you.

INTRODUCTION OF WITNESSES

On my left is Mr. William Fitzsimmons, our Executive Officer; Mr. Richard Pine, our Budget Officer; Dr. Ruth Kirschstein; and Mr. Bill Beldon, from the Department.

OPENING STATEMENT

Not only has most of what we know about the brain, its function and dysfunction, been discovered during our lifetime, but indeed, most of it has been discovered during the past 10 years, bringing new hope to our brothers and sisters, our parents and children who suffer from mental illnesses. We are fortunate to live in an exciting time for research in these illnesses. Increasingly, this excitement is being captured and conveyed to the American people.

A little over a month ago, the Washington Post health section, you may recall, reviewed the ten successes and the ten disappointments of health research over the past decade. The first success listed in the health advances section was improvements in medication treatments for mental illness. Increasingly, there's a fascination with the miracle of the human brain and behavior, both in the science community, as you heard in earlier testimony, and in the general public.

For example, "Newsweek" magazine, which arrived remarkably enough yesterday, features research on the brain as its cover story. A cover story such as this was inconceivable a generation ago, but this one is only the most recent of a series of magazine covers on neuroscience; the brain; new medications for illness beyond Prozac;

on suicide, you recall we talked about that last year, so-called pills for the mind, particularly clozapine. "Scientific American" recently featured the mind and brain, and "Parade" had an article on surveys about the markedly changing public attitudes toward mental illness. Finally, an article in "Seventeen" magazine addressed the issue of adolescents with depression and suicidal thoughts, and the appropriate treatment of each.

I have earlier provided a broad statement for the record about mental illness in America and the advances funded in large measure by the American people through your appropriations. Rather than review that broad picture, I thought that it would be helpful to focus on specific results of recent funding.

For example, our services research efforts have provided accurate information about just how common mental disorders are and how costly they are to our society. With regard to prevalence, one in ten Americans has a diagnosable mental disorder resulting in some disability in a given year. Approximately 2.8 percent of the population has a severe mental illness, such as schizophrenia, manic depressive illness, major depressive disorder, obsessive compulsive disorder, or panic disorder.

Concerning the issue of cost, we know that mental illnesses account for a quarter of all Social Security disability payments. Direct medical care costs attributable to mental illnesses are roughly $67 billion annually, slightly over 10 percent of the total health care expenditures. Cost savings from effective treatments are substantial, however, as our research has documented in a series of reports to Congress and to this committee.

Schizophrenia is, as you know, a profound illness affecting our capacity to reason, to interpret the world accurately, and to develop accurate hypotheses about the world. It's characterized both by positive symptoms, such as hallucinations and delusions, and by negative symptoms such as apathy.

Brain imaging studies of people with schizophrenia have demonstrated the early onset of abnormally enlarged cerebral ventricles, the fluid-filled spaces in the center of the brain, suggesting that these might result from structural abnormalities in the brain itself. Neuropathology studies of post-mortem tissues have also found subtle abnormalities in the pattern of neurons which suggest that the process of establishing these complex connections in the brain during early development is abnormal.

In the past year, several important additions to this puzzle have been discovered. Specific areas in the temporal limbic structures, a part of the brain associated with basic drives and information processing, were shown to be abnormally small in patients with schizophrenia. Further clues to the abnormal migration of these neurons were found in the study of N–CAM, a cell adhesion molecule.

Finally, basic neuroscience research has given us a critical clue to one of the fundamental puzzles of human development: how do cells know what they are to become and where to go? One cell ultimately becomes the billions of different cells of our body, which nonetheless manage to function together and know what kind of cells they are. The development of complex connections in the brain are particularly miraculous. By studying special sensory nerve cells in the fly, researchers have discovered a protein called NUM, which migrates during division of this nerve cell into only one of the two cells, conveying vital information about what this cell becomes as opposed to what the other cell becomes.

The logical next step, of course, is to identify the specific genetic abnormalities which contribute to abnormal brain development in schizophrenia, and this effort is well underway.

In depression and manic depression, a linkage of bipolar illness with the chromosome 18 has been identified in some families with bipolar illness. Male-female differences in brain function during sad mood states also have been identified, which may contribute to our understanding of why women are particularly vulnerable to depression. An anticonvulsant, valproate, has been shown to be as effective as lithium in the treatment of mania, thus offering a therapeutic alternative to individuals who can't tolerate or do not respond to lithium.

Obsessive compulsive disorder in children has been linked to both Gilles de la Tourette's syndrome and to Sydenham's chorea, suggesting that streptococcal infections may trigger an autoimmune reaction in the brain in some disorders, leading to obsessive-compulsive symptoms.

Genetic factors have been shown to contribute to a susceptibility to post-traumatic stress disorder, contributing to our eventual understanding of why different people react differently to the profound trauma of abuse, assault, or war experiences, all of which may result in post-traumatic stress disorder.

In eating disorders, significant differences have been shown in the appetite for and the metabolism of food in patients with anorexia nervosa, as compared with bulimia, even after weight has been regained. These fundamental differences in the regulation of appetite may account for the significant differences in treatment responses, particularly the differences in response to medication of persons with these two disorders.

In infancy, Gaucher's disease is a devastating neuropsychiatric condition caused by a specific genetic abnormality. In addition, a mouse model of this disease has been developed, which has helped diagnose infants at birth and helped determine that this abnormality is more common than previously thought. Our intramural research program, working together with industry, is collaborating on a modification of an enzyme that is used to treat the disease. The enzyme, glucose cerebrocidase, currently costs approximately a quarter of a million dollars per person, per year, to treat this inherited deficiency. A successful modification of this enzyme may reduce those costs substantially by making the replacement enzyme more effective.

And in the elderly, researchers will report this week that the ApoE4 isozyme, a known risk factor for Alzheimer's disease, results in changes in brain function that are evident in brain imaging studies well before the clinical onset of Alzheimer's disease.

These brief summaries capture only part of the excitement surrounding this broad array of research efforts. What they don't capture is the impact of the research on Americans who suffer from mental illnesses. You heard earlier in these hearings, I believe, from Susan Dime-Meenam about the profound effects of manic-depressive illness on her life, and about the benefits of active treatment, effective treatment, derived from research.

You might equally well have heard from other noteworthy individuals who have stepped forward to talk about their experiences with mental illness, whether it be William Styron, Art Buchwald, Dick Cavett, Mike Wallace, Francis Lear, Barbara Bush, Patty Duke, Kathy Cronkite, Willard Scott, Lawton Chiles—the list is extensive. You could not hear, unfortunately from Vince Foster or John Wilson, who died of their own hands, giving evidence that these disorders can be fatal in 10 to 25 percent of individuals with depression or schizophrenia.

Equally touching would have been testimony from Brandon Fitch, whom I heard speak at a convention of the National Alliance for the Mentally Ill. He conveyed the pain of having schizophrenia and the remarkable improvement in his symptoms after the discovery and initiation of clozapine treatment, treatment which converted an essentially non-functioning individual into a speaker at a national convention.

In fact, there are millions of potential witnesses who could come before you and sit in this chair and describe the benefits of research. They would be our relatives and our neighbors, and they could be in fact my relatives. For two of my relatives in the last two generations, the advances came too late. They died of suicide. But several other relatives from my parents' generation and from mine could testify to their distress and to the relief they received from treatment. These benefits are, however, imperfect. We can relieve many symptoms, but causes and cures emerge only gradually. Research is vital.

Thank you.

[The prepared statement and biography of Dr. Rex Cowdry follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Acting Director
National Institute of Mental Health

It is my pleasure to appear before you to discuss the research programs of the National Institute of Mental Health (NIMH).

Let me note that the 1996 budget year will mark the 50th anniversary of NIMH's authorization as one of the original NIH institutes. The defining mission of NIMH is a scientific focus on understanding, treating, and preventing mental disorders. Over five decades, research supported and conducted by NIMH has defined the core symptoms of the severe mental illnesses, including schizophrenia, manic depressive illness, and major depression; has shown that these and other mental illnesses involve specific brain dysfunctions; and has contributed directly to developing an array of effective treatments, including both medications and specific psychotherapies.

Research has shown that mental illnesses are just that — illnesses. They are diagnosable, they produce substantial disability, and they can be fatal. Increasingly, research shows specific biological abnormalities associated with these illnesses.

Research has shown that mental illnesses are common — approximately one in 10 adults experiences mental illness with some disability during the course of a year. Mental illnesses also have profound social and economic impact. The Social Security Administration reported in its 1991 Annual Statistical Supplement that, in 1990, individuals with the most severe illnesses claimed 25 percent of all Federal SSI and SSDI disability payments; these persons are represented disproportionately, moreover, among the homeless and among completed suicides. The National Advisory Mental Health Council, in its 1992 report on Health Care Reform for Americans with Severe Mental Illnesses, which was submitted to the Senate Committee on Appropriations, calculated that the severe mental illnesses cost the Nation $27 billion annually in direct treatment costs, and an estimated $47 billion more for the costs of social service and disability payments made to patients, and for lost productivity and premature mortality.

Research has resulted in effective, highly specific treatments for discrete mental illness diagnoses. Extraordinary advances have been made in developing medications which can provide dramatic relief from the symptoms of manic depressive illness, schizophrenia, panic and anxiety disorders, bulimia, obsessive-compulsive disorder, and attention deficit disorder. Research has established, as well, the efficacy of biological treatments that do not involve medications, such as phototherapy for seasonal affective disorder. And rigorous, multi-site studies supported by NIMH have demonstrated the effectiveness of specific psychotherapies and rehabilitation programs.

Such treatments are not only clinically effective, but also are cost effective. In a paper to appear in the Archives of General Psychiatry, data from which was cited in Science magazine last year, Dr. Richard Wyatt calculated that lithium therapy for manic depressive illness has saved the U.S. economy more than $145 billion since 1970 in reduced clinical costs and the continued productivity of persons with the illness. Clozapine, now used in treating patients with schizophrenia, is saving an average of $23,000 in treatment costs per patient each year, largely by reducing need for hospitalization and enhancing patients' capacities to engage in the activities of daily living, according to analyses reported by Dr. Herbert Meltzer and colleagues in the American Journal of Psychiatry in 1993.

Importantly, in these various accomplishments--that is, in demonstrating the biological underpinnings of mental illness and in developing an array of effective treatments--research has reduced the stigma attached to mental illness.

While any mental disorder presents unique challenges to the ill person and, often, his or her family, we recognize that the most crippling human and economic costs of mental illness are concentrated within 2.8 percent of the population — those approximately 5 million adults with schizophrenia, manic depressive illness, and severe forms of depression, panic disorder, and obsessive compulsive disorder. For these reasons, a comprehensive research program focusing on these illnesses is our highest priority.

To illustrate the breadth of the Institute's efforts to understand severe mental illnesses — efforts spanning basic neuroscience, clinical pathophysiology, and treatment efficacy and effectiveness studies — I would like to focus my remarks primarily on findings from NIMH-funded research on schizophrenia, which remains one of the most formidable challenges to psychiatric science. More than 2 million Americans have schizophrenia in any given year. Typically, the major symptoms of schizophrenia appear in late adolescence or early adulthood. These include both the "positive" symptoms of hallucinations, delusions, and bizarre thought patterns that typically lead to psychiatric treatment and hospitalization, and the "negative" symptoms of social isolation and withdrawal. The illness tends to first appear just as adult life begins, shattering career plans, ending relationships, and tormenting those directly affected and their families and friends. Only a few decades ago, a diagnosis of schizophrenia very often meant that a person would be institutionalized for much of the rest of his or her life.

An increasing number of investigations point with remarkable consistency to the likelihood that schizophrenia is the manifestation of an abnormality in brain development. Evidence for such an abnormality is found in studies of post-mortem tissue of brains from individuals with schizophrenia. Investigators working at an NIMH-supported Center for Neuroscience and Schizophrenia have found that particular populations of neurons normally found in the outer layers of the prefrontal cortex were concentrated instead in deeper layers of the cortex of patients with schizophrenia, suggesting that these neurons had not completed their migration during brain development and may not have made the appropriate connections between the prefrontal cortex and the rest of brain. This developmental abnormality corresponds anatomically to previous reports of reduced activity in the prefrontal cortex in schizophrenia demonstrated by brain imaging.

One of the enduring puzzles of schizophrenia is the appearance of the disease long after the presumed developmental injury. Researchers in NIMH's intramural program now have developed a animal model in which early injury to one part of the brain, the hippocampus, produces behavioral abnormalities which are only evident when the animal approaches adulthood. These behaviors correspond to behavioral abnormalities produced by adult lesions in the prefrontal cortex and elicited by the release of the neurotransmitter dopamine.

Dopamine is the neurotransmitter most closely linked to schizophrenia. Neuroscience researchers have successfully cloned, sequenced, identified, and localized five different receptors for dopamine and now have demonstrated that one of these--the D4 receptor--is elevated in specific brain regions in schizophrenia. A further link in this chain is forged by findings that both clozapine and risperidone, recently introduced second-generation antipsychotic drugs which appear to have particular efficacy against the "negative" symptoms of schizophrenia, are particularly active in blocking this D4 receptor site.

Clinical research shows that these new antipsychotic medications enhance the accessibility of once-intractable patients to community-based treatments. Complementing research on medication efficacy are new services research studies on treatment effectiveness. For example, the NIMH-funded "Assertive Community Treatment" model, a managed care approach to providing severely disabled patients with intensive outpatient treatment, has demonstrated new models of treatment can be effective and at the same time substantially reduce treatment costs. Today, rather than institutionalizing patients for a lifetime, or isolating them in our midst, on city streets, we are increasingly able to offer meaningful rehabilitation and opportunities.

Similar illustrations of research efforts exist for other serious mental illnesses, including mood disorders, anxiety disorders, obsessive-compulsive disorder, and disorders that disproportionately affect certain populations or which are associated with an especially high level of morbidity or mortality, such as eating disorders. Rather than catalog our efforts in all of these areas, I would like to describe briefly our efforts in other priority areas.

The disorders of childhood and adolescence are a longstanding NIMH priority. Preliminary epidemiologic evidence now suggests that about 3 percent of children and adolescents suffer from a severe mental disorder. An urgent need – and a major NIMH initiative begun this year – is research to obtain even more precise data about child mental disorders and their treatment. The just-launched NIMH UNO-CAP study of utilization, needs, outcomes, and costs of mental disorders in the child and adolescent population will enable the Nation to target research, clinical, and service system resources more precisely and efficiently.

While the interests of persons with mental illness ultimately drive all our research, basic science is essential to all progress. Since 1990, NIMH's fundamental research efforts have been instrumental to the United States' Human Brain Project and "Decade of the Brain" agenda. The Human Brain Project is designed to capitalize on the ongoing revolutions in biology and computer science, both to advance the frontiers of mental health research, and to increase the availability of new knowledge to scientists in many disciplines and to the public at large. NIMH works in a coordinated manner with 16 other NIH components in a concerted effort to apply neuroscience to brain and behavioral disorders.

Behavioral research explores factors which shape our interaction with our world, and has a pervasive influence in our society and culture from marketing to education to health care. Just as basic neuroscience research is essential to development of effective biological treatments for mental illnesses, basic behavioral research is essential to the development of effective therapies for depression, panic disorders, phobias, conduct disorders, and the social dysfunction associated with schizophrenia.

Behavioral science research also has been essential in developing and demonstrating the effectiveness of specific programs to reduce the spread of HIV infection. Earlier this year, NIMH convened a research workshop to examine the cost-effectiveness of behavioral AIDS prevention strategies. Behavioral sciences, together with the neurosciences, are helping to identify the many risk factors contributing to the increase in violence in today's society.

As we continue to translate new knowledge into new treatments, we must continue to provide rigorous evidence of the treatments' clinical- and cost effectiveness. Today, when a given treatment is matched appropriately to the needs of a given patient with a severe mental illness, we can anticipate a success rate ranging between 60- and 80-percent, comparable to and, in some cases, exceeding successful treatment outcome rates for general medical procedures. From a cost perspective, the data are unambiguous about the benefits of providing appropriate care to severely ill patients.

Mr. Chairman, I believe that NIMH science represents the best hope that millions of people in this country who suffer from mental illness have for less troubled and disordered lives. Research represents hope for patients' families and loved ones who share in suffering the pain of mental illness.

The President's budget request responds to immediate research needs, including those which have been identified by the Congress and our National Advisory Council. And the request anticipates opportunities emerging in the neurosciences and in basic behavioral science; in patient-oriented, clinical research on mental illness; and in mental health services research.

We are requesting $558,580,000 for fiscal year 1996.

Thank you Mr. Chairman. I will be pleased to answer any questions.

CURRICULUM VITAE
REX WILLIAM COWDRY, M.D.

EDUCATION:

1968: A.B. - Yale College, (Psychology)
1973: M.D. - Harvard Medical School
1973: M.P.H. - Harvard School of Public Health

LICENSED to practice Medicine, District of Columbia (1978-), Commonwealth of Virginia (1977-).

PROFESSIONAL EXPERIENCE:

1973-1976: Resident in Psychiatry, Massachusetts Mental Health Center, Boston
1975-1976: Consultant, Washingtonian Center for the Addictions, Boston
1977-1978: Consultant, Mount Vernon Center for Community Mental Health, Alexandria, VA
1977-1981: Personal Psychoanalysis
1977- -- : Private practice (part-time)
1978- -- : Department of Psychiatry, Georgetown University School of Medicine
  Assistant Professor of Psychiatry (1978-1979)
  Assistant Clinical Professor of Psychiatry (1979-1983)
  Associate Clinical Professor of Psychiatry (1983-present)
1976- -- : Intramural Research Program, National Institute of Mental Health (NIMH)
  Staff Psychiatrist (1976-1982)
  Chief, Outpatient Depression Studies (1978-1981)
  Chief, Borderline Personality Disorders Study (1982-1987)
  Associate Clinical Director for Outpatient Studies (1982-1983)
  Clinical Director (1984-1987)
1984-1987: Medical Board, The Warren Grant Magnusen Clinical Center, NIH
  Chairman, Budget Committee (1985-1986)
  Chairman of the Medical Board (1986-87)
1986-1988: Acting Deputy Director, NIMH
1987- -- : Chief Executive Officer, Neuropsychiatric Research Hospital, Intramural Research Program, NIMH
1994- -- : Acting Director, NIMH

FELLOWSHIPS AND AWARDS:

- American Field Service School Program Scholarship (1963-1964)
- United States Presidential Scholar (1964)
- National Science Foundation Summer Research Associate, Yale University (1967, 1968)
- United States Public Health Service Fellowship, Faculty of Medicine, University of Belgrade, Yugoslavia (1972)
- Kennedy Fellow, Interfaculty Program in Medical Ethics, Harvard University (1973)
- Falk Fellow, American Psychiatric Association (1974-1976)
  - Administrator's Award for Meritorious Achievement, Alcohol, Drug Abuse, and Mental Health Administration (1985, 1988)
  - Fellow, American Psychiatric Association (1990)
- Exemplary Psychiatrist Award, National Alliance for the Mentally Ill (1992)

OTHER ACADEMIC AND PROFESSIONAL ACTIVITIES:

Teaching Experience

- Instructor in Psychiatry, Harvard Medical School (1973-1976), (Biostatistics and Psychopharmacology)
- Chief Resident, Service I, Massachusetts Mental Health Center (1975-1976), Clinical and administrative supervision
- Intramural Research Program, NIMH (1976- --), Supervision and seminars for psychiatric residents and fellows; Director of Residency Training (1984-1987)
- Georgetown University School of Medicine (1978-1979), Supervision of individual psychotherapy, seminars in psychopharmacology, case conferences
- George Washington University School of Medicine (1989-1991), Supervision of psychiatric evaluation and treatment

Appointments:

- American Psychiatric Association (1974-present)
  - (1974-76), Committee on Peer Review
  - (1979-81), Committee on the Protection of Human Subjects
  - (1983-85), Task Force on the Effects of Lithium on the Kidney
- ADAMHA Task Force on Regulations Concerning Research Involving the Institutionalized Mentally Disabled (1979-81)

Mr. PORTER. Dr. Cowdry, thank you for your excellent statement. It's going to be necessary, because there is a vote on, to briefly recess until after I vote. So the subcommittee will stand in recess for 15 or 20 minutes.

[Recess.]

TESTIMONY OF NOBEL LAUREATES

Mr. PORTER. The subcommittee will come to order.

Dr. Cowdry, I believe it was Mr. Istook who asked the question of our six Nobel laureates, as to if they could only put resources on two priorities, which would they choose—which was a very good question. A number of them chose mental health. Does that surprise you, and what would—I assume you would agree with that, but why don't you give us your comments on it? [Laughter.]

Dr. COWDRY. With all deference to the rest of the National Institutes of Health, I wish the question hadn't been posed to the Nobel laureates in quite that way, because it forces a kind of Hobson's choice among remarkable alternatives. Naturally I think that the brain is an extraordinary organ and that our research developments in neuroscience are extraordinarily exciting. The sheer growth in the Society for Neuroscience, for example, is striking. I think the fact that we now have ways of imaging not only the structure of the brain, but also the function of the brain as it relates to mental disorders, is a tremendous opportunity. There are equally valuable opportunities in molecular biology and also in behavioral sciences.

So in answer to the question, we were delighted that the Nobel laureates view our research as a tremendous area of scientific opportunity.

NIMH RESEARCH QUESTIONED

Mr. PORTER. Now, I want to give you an opportunity to respond to some charges that apparently have been made against some of the research being done by the Institute. Members' offices have been receiving mail from listeners to Rush Limbaugh's radio program, where a number of research projects were identified as being funded by your Institute. There is in my hands a news release from Citizens Against Government Waste that apparently takes the same type of studies to task, having a list of them on it. I think you've seen this, I understand you have.

What can you tell us about these research projects and these charges?

Dr. COWDRY. We just heard in the last few days about these charges, and I would like to describe a bit of what we know of the background to this issue. The NIMH portfolio has come under attack in a coordinated campaign, which frankly I would describe as disinformation, initiated by the Citizens Commission on Human Rights. They, I understand, have been visiting Congressmen and they have been planting what I will demonstrate to be misleading information on radio talk shows.

As you may well be aware, the Citizens Commission on Human Rights is a group sponsored by the Church of Scientology and the Commission's campaign echoes the themes of Scientology. Scientologists believe that mental disorders can be treated by an expensive program of so-called auditing, using the E-meter, a device available from the Church of Scientology, to guide the removal of engrams and to advance to higher stages of being.

The church has consistently attacked major advances in psychiatric treatment. They focus particular attention on medications which relieve the profound symptoms of psychosis and of depression. Their latest assault on mental illness research comes under the guise of alleged waste, fraud and abuse. In doing so, they have misrepresented the research programs of the NIMH. There is an underlying self-serving agenda, I believe, that would deny millions of Americans the hard-won fruits of successful treatments resulting from our biomedical and behavioral research.

On the other hand, it seems to me perfectly reasonable that it is the appropriate job of Congress to ask questions about this kind of issue. It is my job to respond to these questions, to defend our research and to explain why we do these studies. I would mention at the outset that in their eagerness to attack NIMH funding, not only have the facts been somewhat distorted and selectively presented by our critics, but there are at least two examples of credibility problems with this information. For example, of the 13 grants that were listed on the executive summary we saw yesterday, almost half aren't even grants of the NIMH. In the most egregious example of misrepresentation, they claim that we funded a "four-year study in which known child molesters were allowed to prey on children without law enforcement officials being notified."

In truth, this study concerns a sex offender assessment and treatment study that was conducted at the Florida Mental Health Group in Tampa, under the direction of Richard Laws. It's one of five treatment programs for sex offenders in the Tampa area. The programs were approved by local authorities to treat child molesters who were required to receive such treatment as a condition of probation or parole. Obviously, these sex offenders were all known to the local legal authorities. Irrespective of the NIMH research component of the programs, the offenders would all be in the community in any case and they'd all be receiving treatment through one of the other locally approved programs.

Rather than endangering the community, I think you can make a strong case that the NIMH research program probably contributed to enhanced safety in this setting by offering the best available treatment in a well-organized, intensive and extended format. By carefully monitoring the participants in the research program, the risk of re-offending by a participating child molester was probably reduced. The research protocol did allow the possibility of intervening in various ways, including notifying authorities in a manner that could lead to involuntarily committing an individual again for violation.

This project had a local advisory board of victim advocates, attorneys, police and others, who carefully reviewed and supported the procedures in this project. In addition, the Tampa Daily newspaper twice produced editorials that supported the research. One editorial is headed "Scientologists way off base in blasting pedophile program."

It is this kind of misrepresentation of facts and the purpose of the research that I think frankly characterize a good many of the specific materials developed by the Scientologists. On the other hand, I can readily understand from the descriptions that were provided by the Scientologists why groups concerned with waste, fraud and abuse might ask what is going on here.

LIST OF QUESTIONED PROJECTS

Mr. PORTER. Well, let's do this. You have this list attached to the Citizens Against Government Waste press release, do you? Let's see, yes, I've been working from a previous list. I think what I'd like you to do, in the interests of finding out the truth, is to go through these and tell me which ones aren't NIMH to start with.

Dr. COWDRY. These all are NIMH projects in today's new list.

Mr. PORTER. We were dealing with an executive summary.

Dr. COWDRY. Yes, the other executive summary——

Mr. PORTER. So these all are?

Dr. COWDRY. Yes.

Mr. PORTER. Okay, do you want to detail any of these for us to tell us about them?

Dr. COWDRY. Certainly. Are there any that would be of particular interest to any of the Members?

Mr. PORTER. I'd just start at the top, and tell me what they are.

Dr. COWDRY. I must tell you, in advance, we have had only about 24 hours to study these charges and I haven't studied the summary statements in great detail. However, I will give you the best information that I have today and respond in more detail for the record in as much detail as the committee would like.

This first study is summarized as being a study of the jaw muscles of pigeons. Actually, the study of the jaw muscles is but a small component of this study. Nevertheless pigeons happen to be an excellent animal in which one can pursue the biological foundations of eating and develop an animal model to study the motivation to eat, the patterns of eating, and specifically the state of motivation. Interestingly, by measuring the pigeon jaw muscle, you can assess their very distinctive responses when their appetite is elevated.

Obviously, animal models in general have been vital to the progress of much biomedical research.

If I could take a moment, I would like to make a more general comment about the characteristics of these studies. Would that be all right?

Mr. PORTER. Surely.

Dr. COWDRY. For many of these grants, I think first you have to believe that the factors that motivate and control sexual behavior are worth knowing about. I believe they are and I think that such examples as the AIDS epidemic, pedophilia, child sexual abuse in general and rape, would in themselves give ample reason to know more about what controls sexual behavior.

For some of the grants, you have to believe that knowing more about how men and women are both similar and different is important, as is understanding the effects of these differences on ordinary abilities, and on diseases such as depression. You have to believe these are worthy of study. The plain fact is that sex hormones are a major determinant of how the brain develops in both human beings and in animals. In addition, the effect of sex hormones on the functioning of the brain is also critical. Men and women do have some tendency toward somewhat different skills, somewhat different behavior, somewhat different strengths, and somewhat different patterns of brain function and animal models are a distinctive, useful way to look at these differences.

I could also provide a few examples which might initially be considered "waste, fraud and abuse" such as research on the giant squid axon—a silly idea, until you understand that the giant squid axon has unique characteristics, and that by studying these we have learned the key factors that control the ability of a nerve to transmit a signal. Much of both mental illness research and neurological research derive from these studies of how the giant squid axon functions.

Or how about a study of the bursa of Fabricius in the chicken? It sounds like a crazy idea. But it led to discoveries that there are two different types of lymphocytes that are involved in immune function. One derives from the B cell in the bursa of Fabricius, or, in the human being, different structures. These B cells are different from T cells, and I need hardly point out the relevance of that to AIDS research. What about studies of monkeys relating to terrycloth mothers? This also sounds silly until you first study this research in freshman year psychology textbooks and then later understand that this kind of research has led directly to interventions with premature infants in incubators. These interventions demonstrate that providing human infants with early human contact in sterile settings, will not only improve their development, but also get them out of the hospital faster, and save money in the treatment of prematurity.

The salivary gland of the fruit fly is another example. The fruit fly's salivary gland has unique giant chromosomes that have contributed to our understanding of genes and their function. How about the special sensory hairs of the fruit fly? A recent cover story of "Cell" magazine explained how sensory hairs have given us crucial information about how cells know where they are going, what they are destined to become, and how they make connections with one another.

As in each of these examples, I bet that everyone on this committee knows how easy it is to turn something worthwhile into a one-sentence summary that makes it look silly and ridiculous. Each of us has had to spend a page responding to one sentence of distortion. I think that is part of what we see here and we will be happy to supply you with those pages for each and every one of the grants that you're interested in.

NATURE OF ATTACK ON NIMH

Mr. PORTER. Do you see this as an attack on scientific research in general, or an attack on your Institute specifically?

Dr. COWDRY. First of all, I think we need to differentiate the reasons people may have for doing this. This committee should reasonably ask questions, given what you have seen printed about the purpose of these grants. The way they've been presented, I would ask question myself about them. My wife, when she saw the list, asked questions about them.

Similarly, the Committee on Government Waste, is that the——

Mr. PORTER. Citizens Against Government Waste.

Dr. COWDRY. I can understand why they would ask questions. Since the original source of these charges came from the Scientologists, I interpret the original effort as an intentional attack, a campaign against mental health, mental illness, and psychiatry.

TRANSSEXUAL AND HISPANIC CENTER STUDIES

Mr. PORTER. It is interesting to me in looking at the list attached to the press release that all but two of them involve animal studies of one type or another. I think the only two that don't are the ones on transsexuals and the one on Puerto Ricans. Putting the others aside for a minute, why don't you comment upon those two, and then I'm sure maybe other Members of the subcommittee have other questions.

Dr. COWDRY. I'd be delighted to. I can't tell you about the transsexual study, because I haven't yet reviewed that study in detail. That was obviously a very small grant of only about $7,000. I'll be happy to supply that for the record.

[The information follows:]

In 1979, Dr. Michael Z. Fleming of Boston University was awarded $7,000 for a one-year period only under NIMH's "Small Grant" program to study the psychology of transsexuals. At the time, transsexualism was defined in the American Psychiatric Association's *Diagnostic and Statistical Manual III,* as one of a group of gender identity disorders about which relatively little was known. Dr. Fleming had access to a unique group of patients at a gender identity clinic, a number of whom chose to undergo sex change surgery. Dr. Fleming's findings, which have significance to those responsible for counseling individuals with gender identity problems, were published in three separate scientific journal articles.

Dr. COWDRY. The allegation that NIMH has supported a 17-year New York study of slang terms used by Puerto Ricans when under stress is an outrageous summary of our Hispanic Research Center located at Fordham University, in the Bronx. Outrageous. In reality, this is a longstanding study of acculturation, particularly of Puerto Ricans, but now expanded to other Hispanic populations, in the New York area, especially in the Bronx. Fordham University has a particular history of excellent relations with the community, as I understand it. The Fordham study is looking at the the process of Puerto Ricans coming into communities in the New York Area and at the issues of acculturation, of language adaptation and of mental illnesses that develop in that context.

It's also a study of how mental illnesses express themselves in Hispanic populations. What is different and how can those differences in expression lead to diagnostic problems in evaluating and appropriately treating Hispanic individuals? The use of the words "slang terms" is a total distortion of an attempt to study the words that Hispanic individuals use to express psychological distress, which may not be nice, simple diagnostic terms like panic, for example, or even depression, necessarily. We even know that the elderly express depression differently and may complain about different things. And that is certainly true cross-culturally.

The study, for example, looks at how a term like—it wasn't slang terms—"ataque de nervios," which is in some Hispanic cultures, a term that's used to describe a panic-like syndrome. And part of the importance is to understand how such a term as this might be similar to panic, and how it turns out to be a more inclusive term. We must know this to be sure that we deliver the right treatment and accurately diagnose individuals who express their complaints in a particular way.

As a result of these kinds of studies, the most recent version of the American Psychiatric Association diagnostic manual now includes a special section that addresses specifically these cross-cultural issues in the expressions of mental illness as they affect accurate diagnosis and treatment.

Mr. PORTER. Thank you, Dr. Cowdry.

Mr. Istook.

Mr. ISTOOK. Thank you, Mr. Chairman. Let me kind of pick up where you've left off. Frankly, I can appreciate your concern, if any group that does not believe in mental health treatment may be involved in any particular effort. But I frankly think it's totally inappropriate, whether it's Scientology or any other group, to say that the information should be disregarded because you disagree with the source of the information. I found that your comments focused upon that. And I think to an inappropriate degree.

But looking at the information that has been provided to us, let's take what you used about the study of Puerto Ricans, and how they express themselves, and therefore you can properly diagnose a mental health condition. As I understand it, that particular study has been continuing for 17 years, is that accurate?

Dr. COWDRY. Well, I'm looking at the review statement of that. That would be correct, yes.

Mr. ISTOOK. And the study that you mentioned regarding the jaw muscles of pigeons has been going on for 32 years?

Dr. COWDRY. Mr. Istook, clearly one of the things that is a problem——

Mr. ISTOOK. I'm just trying to find out if the facts that they've represented to us are accurate.

Dr. COWDRY. It is correct that a study with that grant number is in its 32nd year.

Mr. ISTOOK. Okay.

Dr. COWDRY. There is no question about that. What that signifies to me is that this is an investigator who has come up every three or four or five years for review, with new ideas and with a track record of research findings that justified continued funding.

So what we see here is a cross-sectional report on where the scientist is now, for example, in his neuroscience research, and where he is now in studying eating behavior and motivation. So it does not mean that this investigator has only been recording pigeon jaws for 32 years, by any means. It means that this is a well-established investigator who has had a remarkable track record. That length of support is highly unusual.

Mr. ISTOOK. And I understand what you say of course that the fact that they may be using the same grant number does not mean the particular items upon which they currently focus were their focus 32 years ago or 17 years ago.

Dr. COWDRY. Absolutely.

SEX OFFENDER TREATMENT STUDY

Mr. ISTOOK. I hope you can appreciate that it does raise a concern over how long does it takes to develop certain information, which will vary tremendously, depending upon what's there. And we're concerned, of course, with the rigor of the review process. For example, you mentioned the Florida Mental Health Institute and the sex offender treatment program.

But as I understand what's been provided to us—this is a copy of a memo to the staff from within this particular program, which reads in part, "do not ask a client about the specifics of any illegal act, e.g., a victim's name or address, description of victim, specific behaviors of a victim, statements by the victim or details of any act that could directly connect the client with a particular crime."

Realizing of course that these are persons who have committed past offenses and may be involved in committing some of the most heinous acts against children, as pedophiles, it is of concern that they're told, you know, don't relate information to law enforcement officials. In fact, if something comes up that appears to be involving the commission of an illegal act against a child, try to steer the conversation away, so that you can further the purpose of the research, even though it may mean that there is an ongoing act of pedophilia and injury to a child. I mean, I think that's a legitimate concern that we should have and that you should have also.

Dr. COWDRY. Absolutely. Now, I must say that I haven't seen it, and I would be interested in looking at it. This is a study that was previously funded, but is not currently funded. I am aware that first of all, this grant did well in peer review, which would not necessarily have reviewed a memo like that. That memo would be part of the clinical implementation. And secondly, this project had the support of a broad-based community board and the Tampa Tribune.

Mr. ISTOOK. Well, of course, you say and of the Tampa Tribune?

Dr. COWDRY. That's my understanding.

Mr. ISTOOK. Is that a newspaper, is that some tribunal?

Dr. COWDRY. I hope that it is a newspaper, it's presented as an editorial.

[The following information was provided subsequent to the hearing:]

[From the Tampa Tribune, Aug. 22, 1986]

EDITORIALS—SCIENTOLOGISTS WAY OFF BASE IN BLASTING PEDOPHILE PROGRAM

The Citizens Commission on Human Rights, a group sponsored by the Church of Scientology, is doing a great disservice to the Florida Mental Health Institute, a state facility based in Tampa.

The "human rights" commission, which works out of the church's national headquarters in Clearwater, has started a national lobbying campaign to halt a federally-funded program at FMHI that seeks to determine the success rate of both psychotherapy and behavior modification in curbing child molestation.

The commission has circulated letters to national lawmakers and Florida PTA groups—letters that contain outlandish accusations about the FMHI program.

The letters, and accompanying petitions labeled "Save Our Children From Child Molesters," call the FMHI program "an outrageous and destructive psychological experiment . . . that uses our own children as human guinea pigs to see what known child molesters will do to them." The letters imply that FHMI releases child molesters into the community to see how many youngsters they will attack.

The letters also attack FMHI for calling child molesters "pedophiles" since the Greek origin of that word is "child lover." And the letters claim that behavior modification has been shown to "create assassins out of people," that "psychiatry has never cured one single child molester," and that the two types of treatment FMHI is using on the child molesters have already been proven ineffective.

Since the "human rights" commission is either unaware of the facts or is purposely ignoring them, we'd like to set the record straight.

First of all, FMHI is not releasing child molesters into the community. The 100 men it plans to work with over the next year will be free men—men who have no legal obligation to do anything about their problem. They will have either completed their prison sentences, be on probation or be seeking help to change their behavior before they run afoul of the law. In other words, these men will be volunteering for the program.

And these are rules the program's director has said will be followed: If any of the participants tell FMHI of a crime they have committed, the crime will be reported to law enforcement officials. And if any of the men talk seriously about molesting a child while participating in the outpatient program, the parents of the child will be warned and the program client will be hospitalized.

Since there are few sex offender treatment programs in Florida—few nationwide, in fact—these men might well receive no treatment at all if the FMHI program didn't exist. And since the typical pedophile is believed to commit 200 to 400 acts of child molestation in a lifetime, helping just 100 men curb their deviant appetites could have a significant impact on the future of many children in this and other Florida communities.

But even more important, the FMHI program is primarily devoted to finding the best treatment for pedophiles, not just one that has some effectiveness. The two treatments that will be tested—behavior modification and traditional psychotherapy—were not just pulled out of a hat. They were chosen after reviews of all previous studies on sexual offender treatment showed that certain applications of those two appeared the most beneficial.

Finally, it was not FMHI that chose the term "pedophiles" for these men. The mental health professionals there are not so heartless or removed from reality to think the actions of child molesters constitute anything but a sick kind of "love." Pedophiles is a word commonly used for child molesters—both by lay persons and authorities.

We hope the "human rights" commission will cease its vicious, unfounded attack on the program at FMHI. Or short of that, that its rantings will fall on deaf ears.

Mr. ISTOOK. Sure. Because I know there are other newspaper clippings that we have had from another newspaper in the area, talking about whether things were reported or not being reported.

But you know, I think the question then comes to, how do you compile and ride herd over the review panels? Because so often, when we have people talk about peer review, I hear stories about well, these are people that get together, whether it be once a year or once every three months or whatever it may be, and do the most cursory review of a small fraction of certain information that's coming. I'm concerned about the rigor of that process.

Dr. KIRSCHSTEIN. Mr. Istook, if I may answer that question.

Mr. ISTOOK. Sure.

PEER REVIEW SYSTEM

Dr. KIRSCHSTEIN. The NIH peer review system is considered by all countries in the world and all the scientists in the United States as the finest system there is. I have personally done three or four studies of it. We study it every ten years.

The way the NIH peer review system works is as follows: we have a series of research grant applications that are submitted to NIH, their assignment for review is then decided upon, not by the officials of the Mental Health Institute, but by an independent NIH organization, called the Division of Research Grants (DRG). DRG staff decide not only which Institute has programmatic responsibility, but also which particular review group should assess each grant application.

The members of the review group are appointed by the Director of NIH, based on their qualifications, for a period of four years and have overlapping terms. These are people who are well-known scientists, with academic appointments and are peers of the applicants. They themselves have had grants in the past or currently have research grants. They are required to review these applications in advance of a meeting at which they spend two to three days. They meet three times a year, reviewing anywhere from 50 to 150 applications during a meeting.

Each grant application is discussed in detail by what are called the primary and secondary reviewer. And then the entire group discusses the application and votes on it. Sometimes as long as one hour or so is spent on a grant application, until a consensus is reached as to whether the application is approved, because it has scientific merit, or not approved, if it is not of sufficient scientific merit. Applications are then rated as to the ones that are the very best, very good, and so on down the line.

The second part of the peer review system is the review by the Advisory Councils of each Institute, which are legislatively required bodies. The Advisory Councils make recommendations based on their second level review, not only as to whether the science has been judged appropriately and the application was properly reviewed by the first group, but as to its importance to the scientific mission of the particular Institute. The Council makes recommendations to the director. No grant application can be paid unless the Advisory Council approves of that happening.

Mr. ISTOOK. Mr. Chairman, I realize I'm exhausting my time. Let me just make a final comment, if I might, on that. Because the process that you are describing involves people that are themselves involved in the process of either working for the programs or working through the Institute, NIMH or a related entity, or themselves receiving grants. They pass upon whether someone else will receive a grant, and they, too, in turn, hope that when their turn comes around, their peers will help them get money.

It reminds me a lot of the way that some things have been properly criticized for how Congress operates, with Members saying, "I'll support your project if you'll support my project." Your description is only involving peer review by people with a personal or professional interest in the system, without anybody being involved that is really taking an outsider's perspective on, is this a proper experiment.

Dr. KIRSCHSTEIN. That's not quite true, sir, because the Advisory Councils are constituted by law to have two-thirds of the members be senior statesmen scientists, and one-third be lay members, people from the public who sit on the Councils and determine what is important from the point of view of the American public.

Mr. ISTOOK. Thanks for making that correction.

Mr. Chairman, I know my time is exhausted. Thank you.

Mr. PORTER. Thank you, Mr. Istook.

Now, Ms. Pelosi.

SUPPORT FOR NIMH RESEARCH

Ms. PELOSI. Thank you, Mr. Chairman.

Welcome to our distinguished panel. Dr. Cowdry, I was very impressed by your statement, I'm sorry I wasn't here to hear you deliver it. But we have some big doings on the floor today.

In any event, I was particularly impressed by your statement because we had the wonderful opportunity to hear from a number—was it six, Mr. Chairman—Nobel laureates. And when Mr. Istook asked a question about which areas they would choose if resources were so limited that they could only have two, at least two of them responded that they would invest in mental illness research. And I see that in your defining mission, NIMH has a scientific focus on understanding, treating and preventing mental disorders. We know that. But your further explanation of what you are doing in terms of various therapies and also relating it to the biomedical research is very important.

I was stunned to see the figure that approximately one in ten adults experiences mental illness with some disability during the course of a year. I would say from the standpoint of need, from the standpoint of your missions, from the standpoint of the great scientists who came before us, your work is indeed very important, very necessary, and I think very successful.

I understand that the behavioral science task force of the National Advisory Mental Health Council recently completed a review of basic behavioral and psychosocial research at NIMH. Because of the high cost of mental disorders in this country in terms of treatment, loss of productivity and human suffering, this kind of basic research stands to have a big payoff by increasing our understanding of these disorders, and how to prevent them and how to treat them most effectively.

Could you tell us a little bit more about how NIMH plans to respond to the report's recommendations?

BEHAVIORAL RESEARCH TASK FORCE

Dr. COWDRY. Absolutely. Thank you very much for your comments. I would very much like to report on the history of behavioral research at the NIMH and NIH. I think that in mental illness in particular, we have a series of biological interventions and we also have an array of therapeutic psychosocial or behavioral interventions. The best treatments are emerging from a series of studies of depression, of panic disorder, of true clinical studies that compare biological intervention and psychological interventions. Based on this kind of behavioral research and the combination, it is very clear in each of these, where that's been tested, that the combination of psychotherapy or behavioral therapy, structured therapy and medication has distinctive benefits, and that each makes separate contributions.

Now, therapeutics is an end product of behavioral research. At the other end of it is the kind of basic research that's addressed in the report that you mentioned at the outset. We need that kind of understanding, for example, of motivation and how it is controlled; how behavior can be influenced either by patterns of reward or punishment; of how people perceive risk, for example, and how that influences behavior.

These kinds of information have enabled, for example, a credible response to the AIDS epidemic. Clearly one of the problems of AIDS since there is yet no effective treatment, is how to intervene to reduce the terrible financial and personal toll that this disease, as many others, can take.

I might add that behavioral research has made substantial contributions to other kinds of illnesses. Cardiovascular disease, for example—there are several studies now that suggest that behavioral intervention can significantly reduce either the risk of a first heart attack in people who are at risk or the likelihood of a recurrence. Similarly, the work that we've reported before about using structured psychotherapy to extend survival time in breast cancer patients by some 18 months now has been replicated in two other groups with cancer, in, I believe, lymphoma is the one, and I'll be able to supply the other one for the record.

[CLERK'S NOTE: Subsequent to the hearing, melanoma was identified as the other cancer.]

The fact that behavioral interventions can influence the progress of biological conditions like that is, I think, striking, intriguing and a real fruit of this kind of basic research as it gets applied to human disease.

AIDS RESEARCH

Ms. PELOSI. I appreciate that.

Since you mentioned AIDS, I don't want to ask too many questions about what you already have on the record, here. So I'll just say, one of the concerns in the National Commission on AIDS report is that of all the types of AIDS research, social science research is the most underfunded. Various reports have recommended expanded research in behavioral epidemiology, cognitive science, cultural and ethnographic studies, intervention research and mental health research.

What has been the progress within your Institute in addressing these areas of research, and do you have limitations, how serious are your limitations because of the underfunding?

Dr. COWDRY. Well, I think actually we've had a substantial investment in a broad array of behavioral studies, but they're not just one-on-one behavioral studies. They have included, for example, research at the San Francisco AIDS Research Center that has had a focus on how you can intervene in a broader sense in the community at large to change mores, and, through changing attitudes, also change behaviors.

So there's very definitely a social and a community level of intervention as well that is appropriate, that we have supported. We were delighted that the AIDS Commission report as a whole felt that this research was rigorous and appropriate and showing some benefits in dealing with this problem.

PREVENTION RESEARCH

Ms. PELOSI. Just to follow up on that, last year the Institute of Medicine released their report on reducing mental disorders, "Frontiers For Prevention Intervention Research," a report completed at the request of Congress. According to the IOM, a major effort is needed to study the prevention of mental disorders. How is NIMH responding to recommendations contained in the IOM report?

Dr. COWDRY. Well, there is a procedural response, and then there is sort of a personal response. There are actually two reports. We are in the process of integrating the recommendations of those two. We have made a major push to increase prevention intervention studies in a couple of areas, including depression, and in the treatment of aggressive behavior and potentially aggressive behavior in schoolchildren. We are studying in a rigorous way how that could be done.

I think the opportunities for dramatic expansion of this are obviously going to be somewhat limited by the constraints that we are all under.

Now, I must also say that my first response to prevention, when I'd been the Acting NIMH Deputy Director about nine years ago, and then went back to the Saint Elizabeths Hospital and didn't see much prevention research in the intervening time, I was amazed. I mean, prevention research at that time really was sort of loose, not rigorous as it is today.

Since coming back, I, like many of the basic scientists, including molecular biology researchers, who were on that IOM panel, am convinced that this field actually has made dramatic improvements in the design of trials and in their rigor. There are dose response studies to see what degree of intervention is necessary to produce behavioral change in children who have a tendency to be aggressive in school, for example. The field has made remarkable advances in the past eight years. We hope to continue along that course.

Ms. PELOSI. Thank you very much for your fine response and your excellent work.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you.

Mr. Bonilla.

QUESTIONABLE STUDIES

Mr. BONILLA. Thank you, Chairman.

Doctor, I'd just like to start off by saying I take a back seat to no one in supporting the research at NIH, and I'm very proud of that record. These grants that we're all discussing today certainly shed some questionable light on some of the money that's being funneled through NIH. So I'm glad to hear, at least as I walked in during your testimony, that you were already trying to address that. And I certainly do not expect you to keep track of over 1,200 research grants that your Institute is responsible for.

My line of questioning is going to fall in the category of what we've been discussing already. Are you familiar, or do you know how long the CRISP system has been around, the Computer Retrieval of Information on Scientific Projects system?

Dr. COWDRY. I don't.

Dr. KIRSCHSTEIN. It's at least 20 years, but we think it might be more. We'll supply the actual period of time for the record, sir.

[The information follows:]

The CRISP System in machine-readable form began in fiscal year 1972 and has, therefore, been in existence for 23 years.

NATURE OF INVESTIGATIONS AND PROJECT LENGTH

Mr. BONILLA. Well, using that system, I've been provided with some interesting abstracts on some of the research projects that we've discussed here already. Understanding that abstracts are written sometimes so that only scientists can understand them, I need a little clarification about the exact need for some of the research.

I would appreciate it if you could provide for the record what characteristics the following animals have in common with humans: unisex whiptail lizards, monkeys, rats, red wing blackbirds, tree frogs, pigeons, horses, quail, hamsters, guinea pigs, ferrets, gerbils and the golden mantled ground squirrel. Now, understanding that research involving animals is very important to human research, you can see that we're pushing the envelope, here, it seems, on some of these projects.

And the reason for me asking for this is to try to make sure that we're not wasting any valuable dollars that could be going to something more useful, like cancer research or heart disease or AIDS or whatever else we need to take care of. So I'd appreciate if it you could do that.

How long does research need to be done, Doctor, before NIMH decides to terminate research? I know my colleague, Mr. Istook, was asking about studies that span decades. And so my question is, how long does it take to figure out whether something's useful or not?

Dr. COWDRY. There's sort of an old saw that the correct answer is the one that stops the questions. And in a sense, one of the glories of science is that generally, each answer does in fact lead to a new area that is not understood. The issue for us as a science agency, and for you as the Congress, is tying those new questions to the scientific opportunities and also to assure that there isn't any kind of waste, fraud and abuse.

[The following information was provided subsequent to the hearing:]

Eighty percent of the NIMH grant portfolio has been funded for 7 years or less with the average life span of a grant being 4 years.

And I want to be sure that it is understood that I think for this committee to ask questions like this is totally appropriate. And it's totally appropriate for me to provide you with answers about why studying the lizard, the gerbil, the horse, and so forth is appropriate. Indeed a particular animal is selected for a particular study because it is probably the best model that we have for answering questions that for one reason or another are difficult or impossible to study in human beings.

I'm glad the issue of pedophilia came up. A lot of this research deals, as I said, with sexual behavior, and the regulation of sexual behavior. We need this kind of basic research, in order to assess pedophilia appropriately, and hopefully to develop treatments that prevent this kind of abuse that we are all vitally concerned about. Certainly efforts that have been made to treat sex offenders with sex hormones to control their behavior arose out of basic research. It is critical.

In our Violence and Traumatic Stress Research branch, for example, we are equally concerned with the victims of such behaviors, and with the kinds of both biological and psychological changes that this abuse produces. I want to make it clear that I think the questions about these studies you're asking are perfectly appropriate. What I had a problem with was the way our research studies had been compressed in what I think was a misleading way.

HISPANIC RESEARCH CENTER

Mr. BONILLA. And I'm glad you see the benefit, because oftentimes when we're dealing with medical research or defense money, we have to go to town meetings and defend what we're funding. And some of these things I completely understand are perhaps distorted, but we need to get the ones that are not distorted out so that we can get back to the business of what's important here. The more the NIH can help us with that, the better off we're all going to be.

And I'd like to point out, also, that my alma mater, the University of Texas at Austin, has two grants in question, and I have contacted them personally to try to find out what's going on there, and see if they're useful grants. So we're still waiting to hear from them.

The study that I wanted to mention as well and follow up on was—being an American of Hispanic descent, and sympathetic to the needs of Hispanics in this country, I have a problem with this 17 year study of terms, slang or otherwise, for Puerto Ricans in New York City. Has there been a return for the taxpayers' money in this grant, Doctor? Are we finding anything useful?

Sometimes when we appropriate money for diabetes research or heart research, we get a savings back because in the long term, society doesn't have to spend as much for acute problems. But in this particular study in New York City, have we seen anything, any rate of return for that?

Dr. COWDRY. Let me try to clarify, because this is an interesting study, being conducted at a Minority Research Center of the NIH. And it has multiple purposes. Part of the purpose is to conduct research. And as I mentioned, earlier, first of all, it, as it turns out, is not a study of slang terms. And secondly, that part of the study is just starting. It is just being initiated with this iteration of the center's grant.

Now, these Minority Research Center grants are intriguing, because they not only support the research studies, but also serve to build infrastructure for minority research, both about minorities and by minorities. In this case, the Center is at Fordham University, and has been directed initially by Dr. Lloyd Rogler and now by Dr. Orlando Rodriguez. In addition to research, the Center's mission includes individuals to be sensitive to these cultural issues in doing research and to study the kinds of issues in mental illness that can be minority specific, and which can markedly influence how effective the treatment is.

So, the Center has multiple purposes. Judging from what I have read from reviews of it, I think it has been rather successful. It has been productive in its publications. It had produced well-trained individuals, and it has led to an increased understanding of some of the unique aspects of the ways in which some of our minority populations may express symptoms of mental illness.

Mr. BONILLA. I would perhaps, while you're looking at this particular grant, I would suggest maybe reviewing once again the entire operation there. Because if it's helping the taxpayers, great. But if it's not, we really ought to think about eliminating programs that are not useful.

Dr. COWDRY. Absolutely.

SEXUAL BEHAVIOR RESEARCH

Mr. BONILLA. Since you don't mention sexual behavior at all in your testimony or in your budget justification, could you estimate the number of grants awarded in the past two years, Doctor, that deal with sexual behavior?

Dr. COWDRY. Probably not off the cuff. We'll see whether we have that particular cut through it.

I would say that apart from the violence portfolio of the Institute's Violence and Traumatic Stress Research branch, dealing with both offenders and victims, we do relatively little in terms of clinical application. There is certainly a basic NIMH research effort which has, I think in large measure, been captured by this CRISP search that was done to generate the list of grants. It's relatively clear that the term "sexual" was one of the search terms that was used to pull some of these grants out. We will be happy to review that if you would like, and provide that for the record.

It's interesting, the grants involving aspects of sexual behaviors are clearly a rather small proportion of our entire portfolio. If you take the material that we saw that was distributed and look at the marked grants that the group had concerns about, and then read down the other MH, or mental health, NIMH grants, you see that immediately you move off the grant that there was some concern about, you move to research on the psychobiology of event-related potentials, which is brain wave study in schizophrenia; dopamine in chronic anti-psychotic drug treatment; a clinical science research center; research on social roles in depression and variation with age. You can see that these grants are a very small component of the actual portfolio.

[The information follows:]

In FY 1993, 20 research grants, and in FY 1994, 22 research grants were funded examining the biological and neurobiological bases of sexual behavior in animals out of a total of 3,505 grants funded over the two years.

Mr. BONILLA. Again, I walked in when you were going over all these grants that were in question, and I'd appreciate if for the record, maybe another Member has asked already, to give us the Institute's version and your perspective on these. Because these abstracts, again, don't tell the whole story. So we'd appreciate that so we can look at it ourselves and judge it.

Dr. COWDRY. We'd be delighted to do that. Clearly there is general interest in that.

Mr. BONILLA. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Dr. Cowdry, would you also include in that when you prepare it for the record the identification of the grantee, what institution or researcher is handling it.

Dr. COWDRY. Absolutely. Would it be helpful to have——

Mr. PORTER. Time, costs, etc.

Dr. COWDRY. Is there any interest, since there was an expression of interest in the quality of the peer review, we might even get some idea of what that is like as well?

Mr. PORTER. Yes.

[The information follows:]

NIMH'S RESPONSE TO CAGW'S LIST OF RESEARCH GRANTS

The list of NIMH-funded research projects compiled by Citizens Against Government Waste (CAGW) and the Citizen's Commission for Human Rights (CCHR) presents a grossly distorted picture of both the overall NIMH research portfolio and of the individual grants. The list appears to have been developed so as to include research concerned with basic animal behaviors, research involving sexual behaviors, and studies involving sex-related behaviors in animals.

The CAGW/CCHR-listed grants are grouped below by major areas of scientific relevance, and information regarding the funding history of each is provided. Also, the CAGW/CCHR "description" of the research is juxtaposed to a brief, non-technical abstract of each research project. More detailed, technical summaries of the grants in question were provided to the subcommittee and are available from the NIMH.

The mission of the NIMH is to support and conduct research devoted to understanding the causes, treatment, and prevention of mental illness. In order to understand mental illness, it is essential to examine human behavior in all of its complexities. Behavior, including dysfunctional behavior, is influenced by multiple factors: biological, psychological, and environmental factors, acting in combination. To better understand the operation and interaction of these factors, scientists often find it helpful to study animals.

Animals are used for NIMH research because 1) the behavior cannot be ethically studied in humans; or 2) a particular animal species provides a key to understanding an issue too complex to study in humans; or 3) both reasons. Research may focus on animals whose behavior is similar to ours, such as primates. Or, it may focus on animals whose behavior appears to be strikingly different, such as reptiles. In the latter case, a specific species may represent a "natural experiment," illustrating how, for example, the lack of a certain hormone or brain structure affects behavior. In the descriptions that follow, the rationale for selection of a particular animal model is provided where appropriate.

The NIMH takes seriously the right of Americans to know that public funds are being spent carefully and effectively on biomedical and behavioral research. But we must be certain that the work of talented and dedicated scientists is described accurately and its importance is fully understood.

Length of Research Grants

Some members of the subcommittee expressed concern about the duration of some research grants listed below. The following points are relevant to this matter:

- A research project generally has several aims and numerous experiments. As goals are met, the project evolves but a grant's name and number do not change as long as the general topic remains the same. With each competing renewal of the grant, an investigator must show that the original work promised was accomplished, and that new goals are worthy of funding.

- The current funding of NIMH grants is highly competitive and becoming even more so. Only 17 percent of new applications were funded in FY 1994.
- Most NIMH research projects are funded for relatively brief periods. In fact, 80 percent of all NIMH grants in FY 1994 had 7 years of funding or less.
- All grant applications are subjected to two levels of review. The first involves peer review of the proposal's scientific merit by researchers familiar with the proposed area of research. (However, any reviewer with an institutional or personal relationship with the applicant is excluded from considering that application.) The second level of review is conducted by the Institute's advisory council, which includes both scientists and representatives of the lay public.
- After an initial 2- to 5-year period of funding, an investigator may again apply for further funding. This "competing renewal" application is reviewed just like a new grant, with particular attention to productivity over the last funding period. In FY 1994, the success rate for competing renewal applications was only 39 percent, despite the fact that they had been among the most outstanding proposals at their initial review for funding. This highly competitive process assures that only the most outstanding research is funded.
- When, as rarely happens, an applicant has received multiple renewals, each renewal has been reviewed on its own merits. Approval with a fundable "priority score" from peer review indicates that the researcher's efforts have been highly productive, and that the researcher has proposed new efforts which are also regarded as outstanding.

Medications for Mental Illness

Since their introduction some thirty years ago, psychotherapeutic medications have been established as among the most effective approaches to the treatment of mental illness. These medications also have been useful tools for studying mental illness and the basic neurochemical processes of the brain. Two of the grants identified by CAGW/CCHR involve highly productive efforts to design more effective, specific-acting medications, and to understand the circumstances that make these medications effective. The principal investigators on both grants below are leaders in the field, and both of the laboratories have been immensely productive research training sites for young neuroscientists and physician-investigators over the past two to three decades. The two projects include:

Investigator: George K. Aghajanian, M.D., Yale University Medical School

Title: Psychotogenic Drug Action on Chemically Defined Neurons

Status: Active. Support to date: 25 years (FY 1970-1994), R01 and R37. Total $: $3,969,922. Recompeted/Reviewed: FY 1975, 1980, 1985, and 1990.

CAGW says: *"A 25-year study of the effects of psychedelic hallucinogens on the brains of rats. (Over $2.9 million)"*

In Fact: Schizophrenia is the most chronic and disabling of the severe mental disorders. Research continues to develop and refine medications and other treatments that are increasingly effective in relieving the symptoms of patients with schizophrenia, but definitive information regarding the origins of the disorder is urgently needed. Several brain neurotransmitters, including dopamine and serotonin, have been implicated in the development and course of the illness and are a focus of intensive research from a variety of scientific perspectives.

Early in the history of this research, Dr. Aghajanian was primarily interested in defining the neurochemical mechanism of action of the hallucinogenic drug LSD using a well-established rat model of brain function. These studies focused on developing more effective pharmacologic treatments for the psychotic symptoms often associated with LSD use. In the course of this work, other research revealed that the chemical structure of LSD resembles the chemical structure of the brain neurotransmitter serotonin. This finding led Dr. Aghajanian to further explore the relationship between serotonin and psychotic behavior. His aim is to help identify the neurochemical processes involved in schizophrenia and the therapeutic effectiveness of various anti-psychotic drugs.

Thus, the principle thrusts of his current research involve studies of the anatomy, physiology and pharmacology of serotonin-containing brain cells. These contemporary studies formed the foundation for the development of an understanding of the mechanisms of action for the newest class of drugs used to treat schizophrenia, the so-called "atypical antipsychotics." This class includes the widely prescribed medication clozapine (Clozaril), which has been shown to be effective in many patients with schizophrenia who are unresponsive to all other medications. This research did start with a study of LSD but has evolved into work that is central to our understanding of the systems and neurochemicals which play a role in the causes and treatments of schizophrenia.

Investigator:	William H. Morse, Ph.D., Harvard University
Title:	Drug Action on Behavior and Physiological Function
Status:	Active. Support to date: 32 years (FY 1963-1994), R01 and R37. Total $ to grant: $4,077,578. Dr. Kelleher was funded FY 1963 - 1980. Dr. Morse has been funded since FY 1981. Total $ to Dr. Morse: $2,826,095. Recompeted/Reviewed: FY 1970, 1975, 1980, 1983, 1987, and 1992.
CAGW says:	*"A thirty-one year study on how rhesus monkeys react while being tortured while on mind-altering drugs. (Over $2,365,000)"*

In Fact: Dr. Morse's early work on rhesus monkeys focused on examining how medications (such as anti-psychotic and anti-anxiety drugs) that are used therapeutically for their effects on behavior affect both physiological functions (such as blood pressure) and behavior. These monkeys were not tortured. Indeed, NIH requires assurances from all its grantees that animals used in NIH-supported research will be treated humanely. Rhesus monkeys were especially appropriate for these studies because the effects of medications on these animals are reliable indicators of their effects on people. This research also has examined how the responses of individuals to a given pharmacological or behavioral stimulus are shaped by their prior experiences, how physiology and behavior interact, and how those interactions are affected by the medications under study.

His current studies focus on the behavioral and physiological effects of opiate drugs and on evaluating the therapeutic uses of novel opiates. This work cannot be conducted on humans because of the experimental nature of many of the drugs under study. Conducting such integrated physiological and behavioral studies in a single species provides information on the multiple effects of medications; this information can be used to develop safer, more effective pharmacological treatments for humans.

Dr. Morse's research has provided a number of important findings, including the observation that the behavioral effects of drugs depend critically on the individual's past experience and present activity. This information helped in establishing analytic procedures currently being used in many settings to understand how drugs modify behavior. Additionally, the research demonstrated that in animals (as in humans), certain behavioral activities can lead to sustained high blood pressure.

By delineating the brain receptors that respond to particular medications, this program has also contributed to understanding the underlying pharmacologic effects of behaviorally active drugs. In his long history of productive and ground-breaking work, Dr. Morse has introduced many techniques that are now used throughout the world in behavioral and physiological research in primates.

Affective and Anxiety Disorders

Depression and manic-depressive illness profoundly affect about six percent of American adults in any given year, and severe anxiety disorders, which include obsessive-compulsive disorder (OCD), phobias, panic disorder, and post-traumatic stress disorder (PTSD), affect millions more. The estimated cost to society for these disorders is up to $76 billion per year. Despite the availability of an array of highly effective, research-based treatments, including medications, nonpharmacologic "biological" treatments, and psychological therapies, untreated affective disorders continue to play a central role in suicide, in substance abuse, and in other often severe conditions. Anxiety disorders, too, can be severely disabling. Two of the projects cited by CAGW/CCHR involve research on these conditions.

Investigator: Kenneth Kellar, Ph.D., Georgetown University

Title: Electroconvulsive Shock Effects on Brain Receptors

Status: Study completed - last paid in FY 1990. Support: 5 years (FY 1986-1990), R01. Total $: 682,796.

CAGW says: *"A 5-year study in which rats were given electroshock treatment to compare its effect on their brain to drugs."*

In Fact: Electroconvulsive therapy (ECT) is an important and potentially lifesaving treatment--indeed, the treatment of choice--for certain people who are severely depressed, especially those who are suicidal. Unlike antidepressant medications, which can take from days to weeks to lift depressive symptoms, ECT causes immediate improvement, often enough to dramatically reduce the risk of suicide.

The efficacy of ECT in treating severe depression and other mental disorders is well documented. But how it achieves its antidepressant effects on the brain has puzzled researchers. Does it affect the brain as a whole, or through a specific neural circuit or mechanism? Using rats as research subjects, Dr. Kellar has found that electroconvulsive shock (ECS) does not affect large numbers of circuits and receptors in the brain. Rather, like many effective drug treatments, it targets a particular subgroup of brain receptors for certain chemical messengers. This research thus suggests not only how ECT works, but also points to possible underlying causes of severe depression. It suggests that depression is rooted in disturbances of very specific brain circuits, and that ECT, like antidepressant drugs, targets these systems when they become dysfunctional.

Basic research on ECS has contributed to important improvements in the safety and efficacy of electroconvulsive therapy in humans. Collectively, this body of research is enhancing the capacities of clinicians to treat severe mental illnesses, using therapeutic approaches best suited to the needs of individual patients.

Investigator: Michael Davis, Ph.D., Yale University School of Medicine

Title: Anatomy and Pharmacology of Fear-Potentiated Startle

Status: Active. Support to date: 5 years (FY 1991-1995), R37. Total $: $627,082.

CAGW says: *"A four year study in which drugged rats were startled using sound and electric shocks to determine which drugs block the fear mechanism. (Over $300,000)"*

In Fact: Anxiety and panic disorders are widespread and, in their most severe forms, potentially incapacitating mental disorders. A distinguishing characteristic of these disorders is a person's inability to inhibit fears or anxieties, reflecting a problem in a little-understood "fear extinction" mechanism in the brain. This research project was designed to identify and examine the neural underpinnings of fear and anxiety. Toward this end, Dr. Davis successfully developed an animal model, called "fear-potentiated startle (FPS)." Dr. Davis' research and the work of other scientists consistently demonstrate that findings on fear-potentiated startle in rats generalize in almost every detail to fear reactions in humans.

In four years, this research has defined the entire FPS circuit in rat brain. Using a sophisticated battery of neuroanatomical, neurophysiological, and neurochemical techniques that could not be used with human subjects, Dr. Davis is able to track neural impulses from the instant a stimulus is received in the brain, through all neural "relay stations," and on to the initiation of a movement in response to the stimulus. The detailed anatomical and functional description of the FPS response in the rat has given scientists a much clearer picture of which parts of the human brain are involved in fear and anxiety, and thus, where problems may arise that lead to certain anxiety disorders. With this research it may be possible to develop new medications for treating these disorders.

Eating Disorders

Eating disorders such as anorexia nervosa and bulimia nervosa affect up to 4 percent of young women and smaller number of young men. Anorexia is a form of voluntary starvation, and bulimia is characterized by binge eating and purging. Both can be life-threatening. The CAGW/CCHR list included two basic research grants, the principal aim of which involves attempts to understand the behavioral and brain mechanisms that cause such abnormal behavior by studying particular aspects of eating in animals.

Investigator:	Steven Fluharty, Ph.D., University of Pennsylvania
Title:	Neurohumoral Mechanisms of Ingestive Behavior
Status:	Active, but no additional funding since December 1992. Support: 5 years (FY 1989-1993), P01. Total $: 5,852,711. Dr. Epstein was funded in FY 1989 - 1991; Dr. Stellar in FY 1992; and Dr. Fluharty in FY 1993.
CAGW says:	*"A five-year study of the hormonal mechanisms in the brains of rats which make them want to eat salt. (Over $5 million)"*

In Fact: Understanding how the brain controls eating provides valuable knowledge that could lead to better treatments for eating disorders such as anorexia nervosa and bulimia nervosa. To study complex behaviors such as eating, researchers often need to simplify their task by examining individual components of the behavior. Many of the experimental procedures required for such research are impossible to perform on humans; thus, scientists turn to studies of animals--in this case, the rat.

Dr. Fluharty is leading a program project (designed to bring together several scientists to work on a common goal) that is examining brain control of salt appetite in rats. Because salt appetite is a behavior that can be controlled through well-recognized physiological mechanisms, it offers researchers a chance to understand the complete sequence from a physiological requirement (low salt), to motivation (look for salt sources), to identification of a salt source (salt taste), to behavior (eat salt). Insight into how the brain controls one aspect of eating behavior (salt intake) in rats will provide clues about control of other aspects in both rats and humans.

Dr. Fluharty and his collaborators have identified key brain areas that control salt appetite, as well as the specific hormones secreted by the adrenal gland (cortical steroids) that work together in the brain to stimulate salt appetite. They have also shown how genetic and nongenetic factors affect the brain's receptors for cortical steroids as well as other chemical messengers (peptides). In addition to its relevance to eating disorders, the knowledge gained from this study also may provide new clues to preventing hypertension problems associated with certain food cravings.

Investigator: H. Philip Zeigler, Ph.D., Hunter College of CUNY

Title: Neural Control of Behavior

Status: Active. Support to date: 31 years (FY 1964-1994), R01, R37, K05. Total $: $3,230,877. Recompeted/Reviewed: FY 1967, 1970, 1973, 1976, 1979, 1982, 1985, 1988, and 1993.

CAGW says: *"A thirty-two-year study on the chemical reaction in the jaw muscles of pigeons to find reasons for eating disorders in humans. (Over $1,200,000)"*

"A twelve-year study in which the jaw muscles of pigeons and rats were monitored electronically to determine which brain mechanisms could be linked to eating disorders in humans. (Over $545,000)

In Fact: This research is concerned with how the brain controls eating behavior. An understanding of how the central nervous system controls appetite and feeding will lead to better treatments for eating disorders such as anorexia nervosa and bulimia nervosa, and will also contribute to a more general understanding of brain-behavior interactions. Complex behaviors such as eating are known to involve multiple parts of the brain.

At the onset of his career, Dr. Zeigler virtually pioneered the study of the avian brain in learning and motivation. He identified specific structures in the brain which mediate hunger and formulated the notion that there are centers in the brain critical to hunger. In the next dramatic period of discovery, he pioneered the study of small movements to analyze motivation. Dr. Zeigler's work is based on the notion that it is important to examine parts of the system to understand the whole. Also, because it is impossible to study these behaviors at an anatomical and physiological level in humans, another vertebrate model must be used. Nonhuman animals use many of the same neural pathways for behaviors as do humans. An analysis of the jaw muscles of the pigeon allowed Dr. Zeigler to delineate in detail the neural circuitry related to eating and drinking. He has also demonstrated that the same circuits control hunger in mammals. Thus, by exploiting the advantages inherent in research with the feeding system of pigeons, Dr. Zeigler has developed an outstanding animal model for several aspects of more complex human behavior.

Behavioral Disorders

Why do some people become controlled by compulsive behaviors (such as gambling) or impulsive behaviors (such as violence)? Mathematically precise modeling of behavior over many years has had the surprising outcome of providing explanations for abnormal behaviors that were never envisioned in the original investigations.

Investigator:	Howard Rachlin, Ph.D., State University of New York at Stony Brook
Title:	Operant Analysis of Delay & Probability in Choice
Status:	Active. Support to date: 6 years (FY 1989-1994), R01 and R37. Total $: $692,090. Recompeted: FY 1994.
CAGW says:	*"A six-year study on pigeons and humans to determine the response to delayed punishments or rewards when given a decision to make. (Over $500,000)"*

In Fact: Scientists often use mathematical models to help them understand the critical variables in various biological processes. Dr. Rachlin has employed a mathematical model to examine decision-making. His initial equations were based on studies of learning in pigeons, which are able to learn new, highly measurable behaviors that respond sensitively to small changes in the likelihood and timing of rewards such as food. Because humans show many of the same patterns of response to reward and punishment when they learn, Dr. Rachlin tested his model against human behavior in game situations.

This research is directly applicable to decision-making related to eating, alcohol and drug use, and sexual behavior. For example, this mathematical approach has been used to explain the disorder of compulsive gambling. The model predicts which patterns of rewards and punishments will lead to compulsive gambling. This information may suggest new avenues for treating and preventing such behavior.

Hormones and Behavior

Hormones interact with nerve cells in the brain to have a major influence over critical aspects of human behaviors. They drive a wide range of activities including development, courting, mating, parenting, dominance, aggression and group defense. Hormones are also involved in defending against disease (the immune system), responses to stress, and even styles of thinking.

Understanding the interactions of hormones, the brain, and behavior is providing insight into disorders of behavior that are among the most disruptive to human society: violence, rape, incest, and pedophilia.

Investigator: Richard P. Michael, M.D., Ph.D., D.Sc., Emory University School of Medicine

Title: Hormones, Brain and Behavior

Status: Active. Support to date: 24 years (FY 1972-1995), R01. Total $: $2,410,769. Recompeted: FY 1976, 1979, 1984, 1989, 1993.

CAGW says: *"A nineteen-year study of the affectionate, sexual and aggressive responses in monkeys. (Over $1.6 million)"*

"A twenty-three-year study of the sexual odors and social factors which effect (sic) male Asian monkeys. (over $1,760,000)"

In Fact: Macaque monkeys serve as a valuable model for understanding brain-hormone interactions, together with the environmental and social factors that affect them. They resemble humans in their reproductive physiology, brain organization, developmental periods, and complex social relationships. These studies provide the foundation for understanding the basic biological mechanisms underlying sexual and aggressive behavior in higher primates, including humans. Knowledge of the brain mechanisms that control phenomena such as rape, spouse abuse, sexual child abuse, and other types of violent behavior could have enormous societal benefits.

Dr. Michaels' research, performed in macaque monkeys, is providing information about how gonadal hormones such as testosterone (an androgen), estrogen, and progesterone affect sexual, aggressive, and social behaviors; where and how in the brain these effects are mediated; and how they are affected by environmental and social factors. This work has demonstrated the precise brain locations where gonadal hormones exert their behavioral influence, and the metabolic mechanisms underlying that effect. In addition, these studies have revealed that male monkeys show seasonal changes in aggression and levels of androgens. (Statistical analysis of FBI data on violent crimes from many locations in the USA revealed similar patterns in reports of rapes and assaults, with highest rates in summer.) These effects in monkeys appear to be unrelated to temperature, and their relationship to other rhythms in hormonal release and behavior remains to be investigated.

Investigator: Sue C. Carter, Ph.D., University of Maryland

Title: The Physiology of Social Behavior

Status: Active. Support to date: 2 years (FY 1993-1994), K05. Total $: $165,250.

CAGW says: *"A two-year study on the sexual preference and behavior of prairie voles. (Over $150,000)"*

In Fact: An inability to regulate social behavior and form lasting social relationships is a component of many mental illnesses including autism, antisocial personality disorder, social phobias, and pedophilia. Thus, understanding the mechanisms involved in regulating social behaviors and social relationships is essential for determining the causes and treatment of such mental disorders. Many biological and behavioral factors, or systems, appear to be involved in regulating social behavior; these include genes, brain structure, hormonal influences, interpersonal situations, and broader social conditions. To understand fully how social behaviors are regulated, each system must be examined, and its contributory role in regulating social behavior defined.

Dr. Carter is studying the hormonal regulation of social behavior in the prairie vole. Prairie voles are small rodents that naturally exhibit monogamous bonding and two parent nurturing of offspring--social behaviors that are typically found both in New World Primates and in humans. Thus, the prairie vole offers an economical and unique model for studying the physiological mechanisms involved in regulating monogamy and two parental nurturing. The investigator has discovered that two hormones, oxytocin and vasopressin, play key roles in regulating male-female bond formation. In female voles, oxytocin facilitates the formation of partner preferences, an essential component of pair-bonding. In male voles, vasopressin regulates two behavioral components of pair-bonding--the formation of partner preferences and mate guarding, or the physical defense and protection of the female from intruders.

Given that the hormones being studied (oxytocin, vasopressin, and corticosterone) are found in humans, Dr. Carter's work has clear implications for understanding the role of hormonal influences over human abilities to regulate social behaviors and form social relationships.

Investigator: David Crews, Ph.D., University of Texas at Austin

Title: Evolution of Brain Behavior Controlling Mechanisms

Status: Active. Support to date: 9 years (FY 1986-1994), R01 and R37. Total $: $1,448,900. Recompeted/Reviewed: FY 1989 and 1994.

CAGW says: *"A nine-year study of the brain circuits which control mounting and receptive sexual behavior of the unisex whiptail lizard. (over $1.4 million)"*

"A nine-year study on the sexual behavior of lizards (Over $900,000)"

In Fact: The brain mechanisms underlying many complex behaviors have been preserved throughout evolution, thus making animals, including reptiles such as lizards, appropriate choices for research intended ultimately to clarify certain aspects of human behavior. Sexual behavior is a frequent focus of comparative behavioral neuroscience research because reproduction is a central innate behavior in all animals. In this area, as in research on other complex behaviors, it is often most practical to study one carefully defined part of the behavior under scrutiny; accordingly, Dr. Crews' research focuses on hormonal influences on sexual behavior. Unique qualities of various kinds of whiptail lizard make them particularly useful models for studies of the hormonal control of sexual behavior. The species of whiptail lizards used in Dr. Crews' research include parthenogenetic species: that is, animals that reproduce without getting genetic material from partners. Such animals show sexual behavior but each individual animal can play both male and female roles. Thus, these lizards offer unusually apt models in which to study how hormones influence behavior. This work is directly relevant to an understanding of the nature of sexuality and the relationship of behavior to its biological underpinnings.

Dr. Crews' research has demonstrated that behavioral differences observed in animals of the same species need not be based on structural differences in the brain; rather, animals with the same brain structure but different environmental factors will behave differently, a finding that challenges prevailing scientific understanding of animal behavior. Additionally, the research has shown that progesterone, considered to be a female hormone, plays an important role in male sexual behavior. These findings have stimulated reexamination of progesterone's role in human reproductive behavior.

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Investigator: Michael Domjan, Ph.D., University of Texas at Austin

Title: Learning and Reproductive Behavior

Status: Active. Support to date: 8 years (FY 1987-1994), R01 and R37. Total $: $614,472. Recompeted: FY 1990 and 1993.

CAGW says: *"An eight-year study wherein quail were castrated as part of the research on sexual behavior."*

In Fact: Animal studies of the basic mechanisms of learning traditionally have focused on clearly "biological" drives such as hunger or fear. Not until recently have researchers extended studies of learning to the more complex domain of sexual behavior, which usually involves the interaction of biological and social factors. While much research has been conducted on reproductive behavior in animals, such work has focused largely on hormonal influences, but has not addressed how these influences interact with learning.

In contrast to traditional comparative psychological research in these areas, Dr. Domjan's innovative study of learning and reproductive behavior in the Japanese quail, conducted in natural habitat settings, extends the study of learning through a complex response system of reproductive behavior. Though the name, "*Japanese quail*," seems to suggest that this is an exotic bird, it actually is widely studied in the U.S., for several reasons: The birds are inexpensive and easily obtained; their sexual behaviors are readily observed in their natural habitat (unlike, for example, burrowing animals such as rodents); and they have frequent reproductive activity. Because much is known already about the Japanese quail's brain and hormonal mechanisms for sexual behavior, it is a particularly useful model for examining how nonbiological factors, such as learning, interact with hormonal influences on the animal's sex drive. One element of the research involves removal, under anesthesia, of a bird's hormone-producing organs (gonads), to clarify how loss of hormones affects sexual behavior.

This research shows that sexual behavior is not simply driven by hormones, even in animals. Rather, these birds need to learn many of the appropriate cues to mating. Their learning has been shown to interact with their hormonal levels and to lead to, or suppress, sexual behavior. Now in its eighth year of NIMH support, the project is contributing to an enriched understanding of learning processes common to animals and humans; it also is elucidating how learned cues affect reproductive behaviors. By offering the most detailed analysis to date of the role of learning in sexual behavior, the research, in combination with human clinical studies, may contribute to improvements in behavioral and cognitive therapies for human sexual dysfunctions, including those often seen in mental disorders such as clinical depression and anxiety.

Investigator: Pauline Yahr, Ph.D., University of California at Irvine

Title: Hormonal Control of Social Behavior

Status: Active. Support to date: 21 years (FY 1975-1995), R01 and R37. Total $: $2,345,569. Recompeted/Reviewed: FY 1977, 1980, 1984, 1989 and 1994.

CAGW says: *"A twenty-year study of the so-called sexual control center in the brains of gerbils. (Over $1,290,000)."*

In Fact: Differences between men and women's brain function have long been suspected to exist. These gender differences also have been implicated in vulnerability to and manifestation of specific mental illnesses. Only very recently, however, have brain-imaging technologies such as positron emission tomography (PET scans) and magnetic resonance imaging (MRI) made it possible to detect specific physiological or biochemical differences on the basis of gender.

Long before the introduction of these modern brain-imaging technologies, Dr. Yahr, studying rodents, painstakingly established a direct link between the influence of a sex hormone (testosterone) on the structure and function of a specific group of cells in one region of the brain (preoptic area of hypothalamus, or POA), and the control of various male social behaviors. These behaviors included courting and copulation with females; establishing territories; and vying for social status. Twenty years ago this investigator discovered in the gerbil a clear gender difference in the POA, an area known to be involved in the display of sexual behavior by males. The gerbil was thus recognized as an economical and scientifically valid model animal for this research.

Research now has demonstrated that testosterone influences brain development in all vertebrate animal species, including humans, and the POA is important in sexual communication and behaviors. At a time when no other means existed to investigate the influence of gender on early brain development and subsequent adult behavior, Dr. Yahr's groundbreaking research provided a useful animal model for researchers and, as importantly, stimulated new approaches and insights to the scientific study of brain and behavior.

Dr. Yahr's most recent work has been designed to trace the anatomical connections of the POA, so that the entire brain system for influencing sexual behavior can be better understood.

Investigator: Gordon H. Orians, Ph.D., University of Washington

Title: Physiology, Territoriality, and Decision Making
Status: Closed (last paid FY 1993). Support: 6 years (FY 1989-1993), R01. Total $: 518,836. Recompeted: FY 1992.

CAGW says: *"A five-year study of red-winged blackbirds to determine how humans make choices of mates, dwelling, reproductive areas, escape routes and foraging areas. (Over $539,000)"*

In Fact: Human behavior is often shaped by many of the same biological, environmental, and social factors that shape the behavior of nonhuman animals--even those as seemingly remote as birds. For example, both birds and humans stake out and protect their territory, sometimes using aggressive behavior to ward off intruders. Studying flocks of red-winged blackbirds in the wild, this investigator has found that even in these animals, social behavior is based on their making complex evaluations of their environments and their fellow birds. The dominant individuals in a territory know more than their competitors about its resources and escape routes, and have more stable relations with their neighbors. Thus armed, they are more likely to win when their territory is challenged, and are motivated to escalate conflicts. Their aggressive behavior is not simply the result of some individuals' greater ability or readiness to fight.

Other findings from this research have provoked a reassessment of the role of hormones in aggression. Although some studies have found that high testosterone levels contribute to aggressive behavior, this research suggests that high testosterone levels are the result, not the cause of such behavior. In other words, individuals behave aggressively when it is likely to benefit them (for example, in defending their territory), not because they are driven by hormones.

Studies such as this help to reveal the underpinnings of normal aggressive behavior in birds, and can contribute to a more sophisticated understanding of the roots of normal and abnormal aggression in humans.

Neural Basis of Communication

Effective communication is one of the most important elements of normal behavior across all species. In animals, when communication is disrupted, the consequences can be disastrous: cooperation is made more difficult, competition can escalate to violence, courtship is unsuccessful, and the resulting social isolation can lead to further problems. The study of human communication is extremely complex. Accordingly simpler animal models in this area of study are imperative.

Investigator: H. Carl Gerhardt, Ph.D., University of Missouri
Title: Psychobiology and Neuroethology of Sexual Signalling

Status: Active. Support to date: 1 year (FY 1994), K05. Total $: $91,866.

CAGW says: *"A study of tree frogs communicating to their mates to determine the development and maintenance of speech communication in humans. (Over $91,000)"*

In Fact: Many animal species can make and recognize sound and use this ability to guide their behavior with others of their species. For humans, these sounds are manifested in speech--that is, language and dialect patterns that develop from infancy and evolve into a complex system of communication that is influenced both by inborn skills and learned information. Understanding the development and neural basis of speech--which is central to almost all human social interaction--is vital to understanding normal and abnormal human behavior.

When scientists seek to identify the neural bases of complex behaviors such as speech, it is important to remove as many confounding variables as possible--variables such as learning. For this reason, the frog--which develops normal sound production in the absence of exposure to adult frogs--is an excellent model for studying the innate ability of the brain to develop communication skills, and was chosen by Dr. Gerhardt for his research. In the frog, specific nerve cells (neurons) or groups of neurons that play a role in sound production can be identified.

This study focuses on "sexual signalling" because frogs communicate primarily as a guide to mate selection. Recent findings from this line of research include evidence that this auditory method of selecting mates can be regulated by changes in females' hormonal states and can be modified by small genetic alterations. The investigator's research also has shown that neurons in specific brain regions are tuned to respond maximally to specific features of the sounds.

Dr. Gerhardt has shown that some aspects of sound perception are common to all vertebrate auditory systems, thus answering a question that long has dogged this area of basic research: To what extent are human and animal perceptual systems specialized to recognize sounds specific to their own species? Since some human communicative abilities are, in fact, hardwired within the developing brain and do not depend solely on mimicking adults, the findings of this research have important implications for an improved understanding of how humans process acoustic information, including language. Ultimately, this work extends our understanding of human behavior both normal and abnormal.

Miscellaneous

Investigator: Michael Z. Fleming, Ed.D., Boston University

Title: Evaluating Sexual Reassignment Surgery

Status: Study completed in 1979. Support: 1 year (FY 1979), R03. Total $: $7,236.

CAGW says: *"A one-year study to determine why some transsexuals who apply for sex reassignment surgery follow through while others don't. ($7,236)"*

In Fact: The fundamental goal of this research, which was funded under a 1-year, "small grant" mechanism designed for preliminary or exploratory research, was to begin to explore the psychology of patients with "gender dysphoria"--persistent and profound discomfort with their biological sex. Frequently, discomfort was sufficiently severe to interfere with their ability to work and interact socially, and often prompted these persons to seek counseling. This investigator sought to identify personality and other factors capable of accurately differentiating gender dysphoric patients who eventually would obtain sex reassignment surgical procedures from those who would not. The study also entailed post-surgical evaluations designed to assess the self-esteem and other measures of patients' satisfaction with the procedure.

After surgery, female-to-male transsexuals generally tended to be satisfied with their bodies and the extent of surgical treatment seemed to be related to positive body image. These transsexuals were similar to control college males in the distribution of their scores on measures of psychological masculinity, femininity and androgyny. Male-to-female transsexuals were significantly different from both college females and males because of the very high proportion of feminine sex-typed individuals in the transsexual sample. The investigator envisioned that these findings would enhance the efficacy of therapeutic and counselling interventions for these patients.

Investigator: Orlando Rodriguez, Ph.D., (previously Lloyd H. Rogler, Ph.D., 1977-1990), Fordham University

Title: Hispanic Research Center

Status: Active. Support to date: 19 years (FY 1977-1995), R01. Total $ to grant: $7,829,992. Dr.

Rogler was funded FY 1977-1990 and Dr. Rodriguez has been funded FY 1991-1995. Total $ to Dr. Rodriguez: $2,964,111. Recompeted: FY 1982, 1988, 1993.

CAGW says: *"A seventeen year study of slang terms used by Puerto Ricans in New York City when under stress. (4.7 million)"*

In Fact: Puerto Ricans on the mainland and in Puerto Rico are the second largest component of the U.S. Hispanic population (12.6 percent), exceeded only by Mexican Americans (58.1 percent). Research has shown that Puerto Ricans living in the New York City area are at particularly high risk for severe depression, even in comparison to other Hispanic groups. Understanding such mental disorders of U.S. Hispanics and their diagnosis, treatment, and rehabilitation is of fundamental importance to the mental health of this minority population. The Hispanic Center funded by this grant is located at Fordham University in New York City, which has a larger Hispanic population (1.7 million) than any other U.S. city.

The research program of the Center has evolved over time, but has been integrated by common themes. First, there is a pressing need to develop culturally appropriate measures of mental disorders in U.S. Hispanic populations. There has also been a need for research that can assist in the development of culturally sensitive procedures for assessing and treating mental disorders in U.S. Hispanics. The research in this center has developed over more than 15 years. It is now focused on five phases in mental health care delivery: 1) research on the emergence of mental health problems with special reference to migration, other stressful life events and social network resources; 2) research on how mental health services are utilized and factors effecting such utilization; 3) research on the effects of language and other ethnically related differences between Puerto Rican patients and non-Hispanic psychiatrists on the physicians diagnostic processes; 4) research on the development of culturally sensitive therapeutic treatments; and 5) research on the post-treatment adjustment of Hispanic patients.

The specific study referred to in the CAGW document refers to a project concerned with how the interaction between the culture that Puerto Ricans bring with them to the U.S. mainland, and the mainstream U.S. culture they confront, is related to immigrant Puerto Rican psychological wellbeing and distress. The objectives of Dr. Rogler's study are to develop and validate two psychological scales: a measure that will assess biculturality, and a measure of the idioms (such as "ataque nervioso") that Puerto Ricans use to express psychological distress. The methodology being used in

Dr. Rogler's research is a well-validated one for studying cultural patterns in a specific population. It involves collection of data from small focus groups of first-generation and second-generation Puerto Rican immigrants, both male and female. Participants discuss and share their experiences and perceptions concerning: (1) how people are affected by moving to another country in which the culture, customs, and language are different, (2) how Puerto Ricans going through this change express their problems or difficulties, and (3) the emotional and psychological problems for Puerto Ricans that can result.

This comprehensive research center has been the source of innumerable significant findings in its 15 year history. It has examined and documented the mental health status and needs of Puerto Rican children. It has conducted an extensive examination of the intergenerational processes in Puerto Rican families. The study has also delineated alcoholism indicators among Hispanics in New York State and City. Studies of migration and life experiences of Puerto Ricans who do and do not suffer from mental illness provided much needed information on the interaction between this life stress and the onset of mental disorders. Similarly, studies on the relationship between stress, mental health and coping skills in the elderly have been explored. Much needed data on barriers to services faced by Hispanic chronically mentally ill has been gathered. This data is vital to the Nation, the State and the City in setting health delivery systems. An evaluation of culturally sensitive treatment programs for Hispanics in three psychiatric facilities in New York City was also completed, confirming the importance of cultural understanding to making accurate mental health diagnoses.

Investigator: D. Richard Laws, Ph.D., Florida Mental Health Institute, University of South Florida, Tampa,

Title: Prevention of Relapse in Sex Offenders

Status: Study completed 1990. Support: 4 years (FY 1986-1989), R01. Total $: $1,371,914. Dr. Laws was supported FY 1986-1988 ($1,019,623) and Dr. Jenkens-Hall was funded in FY 1989 ($352,291). Recompeted: FY 1989

CAGW says: *"A four-year study in which known child molesters were allowed to prey on children without law enforcement officials being notified. (Over $1,371,000)"*

In Fact: The purpose of this research was to determine whether a coordinated package of behavior therapy techniques designed specifically for use with sex offenders improved the treatment of sex offenders (and thus helped prevent further offenses) when added to standard psychotherapy for these persons.

The research director was D. Richard Laws, Ph.D., a psychologist with more than a decade of experience in treatment and research on sex offenders.

The subjects of the research were adult male sex deviants, primarily pedophiles (child molesters). Of these subjects, 44 percent were referred to the research project by the Probation and Parole Services, Department of Corrections, State of Florida. Thirty-nine percent were referred to the project by mental health clinics, mental health professionals, and attorneys. Seventeen percent were men who came on their own to seek help.

Before the research was initiated, and funded by the NIMH, the goals and purposes of the project were reviewed and approved by:

- Chief of Police, Tampa Police Department
- Regional Administrator, Probation and Parole Services, Region V, Florida Department of Corrections
- Chief Assistant Public Defender, Office of Public Defender, Thirteenth Judicial Circuit, State of Florida
- Speaker Pro Tempore and Chairperson of the Subcommittee on Appropriations for HRS/Criminal Justice, Florida House of Representatives.

The research subjects were of three kinds: men who had completed prison sentences for child molestation; men who had been placed on parole or probation because of child molestation; and men who were voluntarily seeking help.

Since the subjects were men who had molested children or had sexual urges in this direction, protection of children was an overriding concern for this research project. To get the men to come for treatment, they had to be assured that information they gave to researchers about their sexual behaviors would be confidential and would be protected against subpoena. They were told, however, that if they provided details linking them to a specific sex crime this would be reported to the authorities. They were also told that if they posed a risk to an identifiable child, both the authorities and the parents of that child would be notified, and they themselves might be hospitalized. As a further precaution to insure child and community safety at all times, the project was monitored by a community advisory board which had representatives from law enforcement, probation and parole, victims programs, and the sex offender unit in the Florida State Attorney's office. As can be determined, the project resulted in no additional risk to children or the community, and almost certainly reduced risks.

The treatment involved showing men explicit sex materials in order to assess the nature and strength of their deviant sexual interests, including interests they might otherwise conceal. Half of them were given treatment specifically aimed at eliminating deviant sexual urges and preventing relapse; the others received standard psychotherapy.

The project produced two important findings: (1) A coordinated package of behavior therapy techniques designed specifically for use with sex offenders was no more effective than psychotherapy in reducing sexually deviant urges; (2) Relapse prevention was effective for some of the men.

Based in part on the results of this research, Dr. Laws compiled and edited the book Relapse Prevention with Sex Offenders, New York: Guilford Press, 1989. This book was subsequently rated the most influential reference book in its field by the membership of the Association for the Treatment of Sexual Abusers.

Mr. PORTER. Mr. Stokes.

CHILDHOOD MENTAL DISORDERS

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Cowdry, nice to see you.

Doctor, can you tell us, what is the extent of mental illness in children and adolescents in the United States?

Dr. COWDRY. Mr. Stokes, the answer to that has to be yes, and no. We have some rough estimates. But one of the vital things that we have just initiated is in fact a study that will answer exactly the question that you posed. It's called the UNO-CAP study, a study of utilization, needs and outcomes in child and adolescent—I forgot at the moment what the P stands for, but there is a P on it. Populations, of course. Thank you.

The UNO-CAP study has two purposes. Number one is to define the actual prevalence of these disorders in children, both for local populations that span urban and rural areas, and in a national sample as well. In addition, the study will look at how services are provided. It is very clear that there are distinctive unmet needs in treating the children of our Nation who have mental disorders. The one estimate in children is a rough estimate, and it suggests 20 percent. I think that is probably similar to the adult estimate that includes some individuals who are not significantly disabled from a mental disorder.

We'll have more precise answers for you when we have results from UNO–CAP.

Mr. STOKES. Okay, we look forward to that. Now, Doctor, if we were to go back, say, over the last four or five years, would we see an increase or a decrease in mental illness in children, or don't we know?

Dr. COWDRY. We don't know that, sir.

PROZAC

Mr. STOKES. Recently, there's been increased concern about the use and the side effects of Prozac in the treatment of mental illness. Can you tell us whether this is a valid concern or not?

Dr. COWDRY. Certainly. As we know, all medications to treat any illnesses have their benefits and their side effects. And part of the purpose of some of the research which we have conducted, and which certainly the pharmaceutical industry actively is involved in when bringing a drug to market, tries to address risk and benefit.

First of all, in looking at Prozac's effect in definable psychiatric disorders, particularly depression, it's very clear that Prozac is remarkably effective. It is as effective as the standard antidepressants, and it has a different side effect profile that many people find preferable to some of the side effects of drugs like imipramine or amitriptyline or others. So there are some advantages in that it treats conditions that previously available drugs did not treat, and in fact, there's a class of conditions that it treats that may be unique.

Obsessive compulsive disorder, for example, does not respond particularly well to standard antidepressants, but these more serotonergic antidepressants may have a distinctive benefit. The same appears to be true in treating the eating disorder, bulimia nervosa, which appears to show a distinctive response to drugs like Prozac and other serotonergic inhibitors. Panic disorder, although it may respond to other antidepressants and other interventions, is particularly beneficially treated with Prozac. So there are some distinct advantages and some things that set it apart in some ways from previously available drugs.

As you know, concerns have been raised about whether Prozac contributes to suicidal behavior or to violent behavior. The FDA examined that question extensively and concluded that there was no evidence to support that. I don't believe that anyone has been successful in demonstrating that, even in court, let alone in a scientific setting. It's very clear that suicides do occur during treatment for depression. They occur with all antidepressants. The question is, does Prozac, carry a special risk? The answer appears to be no.

PRESCRIBING MEDICATIONS

Mr. STOKES. Some psychiatrists are expressing considerable concern over the possibility of psychoactive medications being prescribed by individuals that do not have the proper medical education and residency training for prescribing these type of prescriptions. They are also emphasizing how important it is for the prescriber to really be knowledgeable about the medication's characteristics and the patient's mental health status. Can you respond to these concerns?

Dr. COWDRY. I don't believe the Institute has an official position on that issue. Clearly we are concerned that anyone prescribing medications knows what they are doing, is aware of physical disorders that may cause an adverse reaction to a medication, understands the actions of the drug, and has sufficient knowledge of the functioning of the human body to understand both the benefits, but particularly the potential risks of a medication and its interaction with other drugs. That's a general answer that doesn't quite answer the question you asked.

Mr. STOKES. I think I understand why. [Laughter.]

EFFECTIVENESS OF MEDICATIONS

Mr. STOKES. Doctor, your opening statement states that when a given treatment is matched approximately to the needs of a given patient with a severe mental illness, we can anticipate a success rate ranging between 60 and 80 percent. This rate is comparable to and in some cases exceeds successful treatment outcome rates for general medical procedures. To what can we attribute this success, and how is the medication so successfully targeted?

Dr. COWDRY. Well, I think I would have to say that the medications that we have now can control the symptoms of these disorders in many individuals, the majority of individuals with, for example, depression, panic disorder, and to some degree schizophrenia. In many individuals, the effects can be truly miraculous. We are understanding better the mechanisms of actions of these drugs, but I don't think that the drugs enable us to get to the root cause of illness.

We do not know the causes. We don't have methods of "curing" these illnesses yet. All we have are ways to reduce symptoms in a majority of individuals with these illnesses. But quite frankly, for recurrent conditions as many of these illnesses are, it's much better to have that than not.

NEUROLOGICAL RESEARCH

Mr. STOKES. Doctor, a couple of weeks ago we had a hearing in this room where several Nobel laureates testified before our subcommittee. On that occasion, they stressed to us that neurological research offered great opportunity in terms of medical advancement and so forth. My question to you is to what degree is neurological research important in terms of your Institute?

Dr. COWDRY. Absolutely vital. If you had to summarize what we do, it is study the brain and behavior, not the brain in isolation. And increasingly, not behavior in isolation, but rather the interaction of those two, and experiences that both influence normal development, so that we can understand the basis for it, and that produce mental illnesses.

MINORITY HEALTH RESEARCH

Mr. STOKES. I'm sure I need not tell you about the concern that I have and have had for some time about the disparity between minority health and majority health in this country, the wide gap between the two. To what degree is your Institute involved in addressing this type of disparity?

Dr. COWDRY. Well, we have a somewhat different situation than is true in some areas, such as the high prevalence of hypertension among Black Americans. It does not appear as though any of the mental disorders are particularly associated with minority status. There is no race-specific or ethnic-group-specific vulnerability to or protection from most of the mental disorders, with the possible exception of eating disorders, particularly anorexia, which may have some differences. What differences do exist in prevalence appear to be associated with socioeconomic status.

So we have a somewhat different issue in terms of predisposition, or what may underlie these differences. We have focused most of our attention on being sure that everyone understands that, in the absence of a research-based dianostic test, mental disorders can be diagnosed only by interview and by behavior. We need to be sure that we've got an accurate bead on factors that enhance diagnostic accuracy, and understand what features of a mental illness may have unique meaning to minority individuals.

Mr. STOKES. Thank you very much, Dr. Cowdry.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you.

Dr. Cowdry, I had a lot of questions on matters other than the ones that we felt we ought to begin with, having received the news release and the charges. Unfortunately, we have three Institutes to complete this afternoon.

So we're going to have to put these questions in the record, which is what I'll do initially. But I may decided that after we come back from the break that should end May 2nd, we will have a short period of time when it may be necessary to ask you to come back and testify again. I feel that we haven't gotten to many of the subjects that I would prefer getting to and discussing. And we simply don't have time to do it today.

So we thank you today for your testimony. I hope that we don't have to call you back, but thank you for the fine job you did today, and the fine job you're doing at NIMH.

Dr. COWDRY. Thank you, Mr. Porter, I'll be at your disposal.

Mr. PORTER. Now, we're going to have to stand in recess briefly. Mr. Bonilla will come back and start us again, and I'll go to vote. The subcommittee stands in recess.

[Recess.]

[The following questions were submitted to be answered for the record:]

RESEARCH FUNDING

Mr. Porter: Identify 1994-1996 spending on the following: schizophrenia, depression, bipolar disorder, panic disorder, youth suicide, Alzheimer's disease, eating disorders, and violence.

Dr. Cowdry: NIMH estimated funding for the specified disorders for FY 1994-1996 follows:

Mental Disorder	FY 1994 Actual	FY 1995 Estimate	FY 1996 Pres. Budget
Schizophrenia..	$110,416,000	$114,359,000	$117,820,000
Depression.....	$127,802,000	$132,556,000	$136,649,000
Bipolar Dis....	$31,749,000	$31,889,000	$33,887,000
Panic Disorder.	$13,565,000	$14,073,000	$14,510,000
Youth Suicide..	$10,371,000	$10,766,000	$11,139,000
Alzheimer's....	$25,210,000	$26,150,000	$26,958,000
Eating Dis.....	$8,740,000	$9,037,000	$9,304,000
Violence.......	$37,993,000	$39,499,000	$40,758,000

INTRAMURAL RESEARCH

Mr. Porter: There have been reports over the past year of morale problems in your Institute--in particular, linked to the downsizing of your intramural research program. Can you tell us what changes you are making to NIMH intramural research, and how you are addressing the concerns that have been raised, especially with regard to clinical research?

Dr. Cowdry: Morale problems that existed in the past are being overcome by the swift actions and changes introduced by the new Acting Scientific Director, Dr. Susan E. Swedo. She established an active advisory committee of associate directors--two basic researchers and 3 clinicians--who are consulted on a regular basis and are aware of each major decision. Dr. Swedo met with each laboratory/branch chief, and they are very supportive of her goals for the Intramural Research Program (IRP). One such goal is to make certain that the superior programs, as evaluated by the Board of Scientific Counselors, have adequate resources to support their scientific investigations and expertise. Another aim is the continuing effort to strengthen collaborations between intramural research groups (i.e. NIMH, National Center for Human Genome Research, National Cancer Institute), and results are starting to be seen. However, I would also like to emphasize our continued commitment to taking corrective action to deal with the few programs that have not been evaluated as truly outstanding through peer review. While these actions may transiently worsen morale in some parts of our program, they are essential to the long-term excellence of the IRP and to responsible management of taxpayer dollars.

To address the morale issue among trainees and to focus on and meet our commitment to their needs, a new training committee was formed. It consists of basic and clinical researchers who will review the quality, scope, and all other aspects of both clinical and basic training and explore ways of enhancing the educational experience in the intramural program.

With regard to clinical research and increasing hospital costs, uncertainty about the extent of future support contributed to the morale problem. Dr. Swedo is working with the Clinical Center to establish a more equitable cost-based system for psychiatric patients who do not require the same level of intensive medical care as cancer or AIDS patients. To begin downsizing, the NIMH became a partner with National Institute on Aging and the National Institute of Neurological Disorders and Stroke in the inter-institute consortium for Alzheimer's disease research which will consolidate all Alzheimer's patients on one ward at the NIH Clinical Center. The IRP reduced its inpatient wards by 20 percent (from 5 to 4) and began a new system for admitting patients which will utilize the available hospital beds more efficiently, resulting in an increase in the average daily census while decreasing costs.

EATING DISORDERS

Mr. Porter: I have a continuing interest in your work on eating disorders. Is it correct that you have had less success in finding treatments for anorexia than bulimia?

Dr. Cowdry: Research has demonstrated the efficacy of several forms of psychotherapy (Cognitive Behavioral Therapy and Interpersonal Therapy), as well as pharmacological agents (Selective Serotonin Reuptake Inhibitors)--which are most effective when used in combination with psychotherapy--for the treatment of bulimia nervosa. Research has yet to document the efficacy of such treatments for anorexia nervosa.

Mr. Porter: The outside community has urged you to begin an education campaign on eating disorders. Your Institute has been reluctant to do so, saying that you don't know enough about the disorders to justify a campaign. How are you developing the knowledge base to make an education campaign possible in the future?

Dr. Cowdry: The NIMH believes it is appropriate and timely to develop an educational campaign on the diagnosis and treatment of eating disorders that is targeted to primary care practitioners and mental health and related professionals. Such a campaign of professional education, however, must be based on sound research knowledge. This past February, the NIMH convened an Eating Disorders Scientific Advisory Group to address the questions of what do we know from research, at what level of confidence do we know it, and what messages emanating from the research do we want to convey to targeted professional audiences. The results of this meeting will serve as the basis for curriculum development and other professional education activities.

SERVICES RESEARCH

Mr. Porter: Is there any truth to the rumors that services research may be reorganized out of NIMH?

Dr. Cowdry: There have been a number of internal government discussions related to possible ways of reorganizing agencies and programs to support the Reinventing Government initiative. Health services research has been one of the topics of discussion, but I am not aware of any formal plan or proposal to move services research out of NIMH.

REINVENTION

Mr. Porter: The organizational chart for your Institute seems to contain many more offices than the typical NIH institute. Are you considering any streamlining as part of your reinventing government efforts?

Dr. Cowdry: The Alcohol, Drug Abuse, and Mental Health Administration Reorganization Act of 1992 (P.L. 102-321), which made the NIMH part of the NIH, also mandated the formal establishment of various positions and offices within the Institute. These include the following:

- Associate Director for Special Populations (designated head of this Associate Director's Office)
- Associate Director for Prevention (designated head of Office on Prevention)
- Office of Rural Mental Health Research
- Office on AIDS

In accordance with an NIH policy requiring that Institute EEO Management Officers report only to the Institute Director, the NIMH has also established a separate Office of Equal Employment Opportunity.

As part of its streamlining efforts, the NIMH is looking at the functions of all of these offices to assure that the functions are accomplished in the most effective and efficient manner possible.

HUMAN BRAIN PROJECT

Mr. Porter: What is the principal goal of the Human Brain Project? How many agencies are supporting this effort, and with what total funding?

Dr. Cowdry: Understanding brain function requires the integration of information from the level of the gene to the level of behavior. At every level there has been an explosion of information with concomitant, and increasing specialization of scientists. The price of this progress and specialization is that it is becoming virtually impossible for any individual researcher to maintain an integrated view of the brain. The Human Brain Project supports research and development of advanced technology carried out in the context of brain and behavioral research. The goal is to develop informational tools to allow brain and behavioral scientists to keep track of, make sense of, and share data generated by tens of thousands of researchers and clinicians. In the long term, the Human Brain Project will provide more than just a sophisticated array of information technologies to help scientists understand how various aspects of brain function fit together. Its tools will also serve as models in other areas of information technology to promote communication and collaboration across scientific disciplines and geographic locations.

NIMH has, so far, recruited fourteen other Federal components to form the Federal Interagency Coordinating Committee on the Human Brain Project. These include: the National Institute on Drug Abuse; the National Institute on Aging; the National Institute of Child Health and Human Development; the National Institute on Deafness and Other Communication Disorders; the National Library of Medicine; the National Heart, Lung, and Blood Institute; the National Institute of Dental Research; the National Institute on Alcohol Abuse and Alcoholism; the Fogarty International Center; the National Institute of Neurological Disorders and Stroke; the National Science Foundation; the Department of Defense Office of Naval Research; the National Aeronautics and Space Administration and the Department of Energy. NIMH spent $2,447,231 in FY 1994 on the Human Brain Project. The Institute expects that funding for FY 1995 will be approximately $3,027,000. Total Federal funding was approximately $5,604,000 in FY 1994.

SCHIZOPHRENIA

Mr. Stokes: According to your opening statement, the medication now used to treat schizophrenia--clozapine--saves an average of $23,000 in treatment costs per patient each year. To what extent are there side effects associated with the long-term usage of this medication?

Dr. Cowdry: Clozapine may cause sedation, excess salivation, and (most seriously) agranulocytosis, a blood disorder in which there is a precipitous drop in white blood cell counts. Agranulocytosis is usually reversible if medication is withdrawn promptly and supportive care is provided for the patient. This is the reason for the mandatory weekly blood tests for patients receiving clozapine. Among 11,555 patients receiving clozapine in the U.S. from February 1990 to May 1991, 73 patients developed agranulocytosis (0.8% at 1 year) and two of these died. The vast majority of cases developed in the first 3 months of treatment, suggesting that monitoring should be most intensive in the first 3-6 months of treatment.

Mr. Stokes: As the Institute approaches its 50th anniversary, what are some of the landmark achievements reached in diagnosing, treating, and preventing schizophrenia?

Dr. Cowdry: There has been a great deal of progress in our understanding of schizophrenia over the past 50 years, due in no small part to research funded by NIMH. While the illness was once attributed to poor parenting or childhood trauma, it is now clear that schizophrenia is a disorder of the brain. This understanding, in turn, has led to the development of rigorous criteria for diagnosing the illness based on symptoms and clinical course. Schizophrenia is characterized by both acute psychosis (e.g., hallucinations, delusions, and other so called "positive" symptoms) and varying degrees of chronic deterioration (e.g., social withdrawal, vocational impairment, and other "negative" symptoms). As well as better delineating the phenomenology of schizophrenia, psychiatric researchers have begun to understand the biological underpinnings of the illness. Modern neuroimaging and psychophysiologic methods have been able to demonstrate specific, albeit subtle, alterations in brain structure and function. Many of the manifestations of schizophrenia likely are tied to dysfunction in specific neural pathways. Further, genetic studies have demonstrated that there is a heritable component to schizophrenia, and efforts are underway to identify the genes responsible.

As well as increasing our understanding of the pathophysiology of schizophrenia, research supported by NIMH and the pharmaceutical industry has led to the development of drugs for treating this disorder. Prior to the introduction of neuroleptic antipsychotic drugs, almost 40 years ago, most patients who developed schizophrenia were consigned to a lifetime of hospitalization in a mental institution. Antipsychotic drugs, while no panacea, now make it possible for the majority of patients with schizophrenia (although not all) to continue to function in society. Understanding how these drugs work in schizophrenia has been an important goal of research. The different brain receptors where antipsychotic drugs act have been identified and their location in the brain mapped. Recently, developments in radiochemistry and neuroradiology have even made it possible to visualize these receptors in vivo, in living humans.

Perhaps the most exciting recent advance is the development and introduction of clozapine, a novel antipsychotic that is effective in at least a third of patients with schizophrenia who previously failed to respond to available antipsychotic drugs. With clozapine as an example, and with our growing knowledge about the neurochemistry of antipsychotic agents, a number of new drugs for treating schizophrenia are being developed, including the recently approved antipsychotic, risperidone.

While we can diagnose and treat schizophrenia, the ultimate goal, preventing the illness, has largely eluded scientists. A number of lines of evidence suggest that schizophrenia may in part, be due to maldevelopment of the brain, and some studies suggest that viral infection during pregnancy or perinatal complications may predispose to development of schizophrenia. Hopefully, a better understanding of the biological etiology of schizophrenia, especially the identification of genetic alterations that make an individual susceptible to schizophrenia will eventually make primary prevention possible. The past 50 years of research have led to stunning advances in our ability to diagnose and treat schizophrenia. Nevertheless, much remains to be learned before this disorder no longer devastates American families.

HIGH PRIORITY

Mr. Stokes: How much is included in the FY 1996 budget for each of the mental illnesses that are considered a high priority for the Institute, and how does the proposed FY 1996 funding level compare with the FY 1995 and 1994 funding levels?

Dr. Cowdry: NIMH considers the entire spectrum of mental illness a high priority. The Institute brings a unique multidisciplinary approach to the study of the human brain and behavior in health and in illness, integrating findings from the neurosciences, basic behavioral sciences, clinical research, epidemiology, prevention research, and mental health services research. NIMH research focuses on the mental health needs of special populations, including people living in rural areas, racial and ethnic minority populations, and women. Within this overall approach, the Institute supports basic research and research addressing the causes of and treatments for specific mental illnesses, for example, schizophrenia, depressive disorders, anxiety and panic disorders, Alzheimer's disease, eating disorders, and childhood mental illnesses. Funding for these disorders is as follows:

Mental Disorder	FY 1994 Actual	FY 1995 Estimate	FY 1996 Pres. Budget
Schizophrenia...	$110,416,000	$114,359,000	$117,820,000
Depression......	$127,802,000	$132,556,000	$136,649,000
Anxiety disorder	$36,211,000	$37,631,000	$38,824,000
Panic disorder..	$13,565,000	$14,073,000	$14,510,000
Alzheimer's.....	$25,210,000	$26,150,000	$26,958,000
Eating Disorders	$8,740,000	$9,037,000	$9,304,000
Child disorders.	$150,351,000	$156,224,000	$161,166,000

NEW ANIMAL MODEL

Mr. Stokes: What is the significance of the Institute's intramural researchers' development of the animal model which appears to detect early injury to the brain? How will this model be used to further advances in this area of research?

Dr. Cowdry: One of the mysteries of schizophrenia is how abnormalities which appear to be a result of either early developmental aberrations or early injury could become clinically apparent only after puberty. An animal model of delayed behavioral abnormalities following early injury has been developed by NIMH intramural researchers using excitotoxic lesions of the ventral hippocampus (VH) in neonatal rats. These lesions produce abnormal behavioral responses to dopamine agonists and to stress which only become apparent after puberty and which differ from those in rats with VH lesions in adulthood. Other findings, though at a preliminary stage, show that several factors, including genetic program (represented by genetically inbred rat strains), the extent of hippocampal damage, and environmental/pharmacological stimuli may affect behavioral patterns associated with neonatal hippocampal defect. The significance of this is that this neonatal excitotoxic hippocampal damage in the rat may serve as a potential model for schizophrenia since it reproduces multiple aspects of this illness. This animal model may be potentially useful for studying pathophysiological mechanisms of schizophrenia and for developing new therapies.

CHILD AND ADOLESCENT MENTAL HEALTH SERVICE NEEDS

Mr. Stokes: When are results expected from the newly implemented UNO-CAP study? How did this project evolve, and what is the estimated cost?

Dr. Cowdry: Since the mid 1980's, when the NIMH Epidemiologic Catchment Area Study provided valuable new data on the prevalence of psychiatric disorder risk factors, and service needs in adults, there has been interest in developing a similar study of child and adolescent mental health service needs. The Institute of Medicine's report, Research on Children and Adolescents with Mental, Behavioral, and Developmental Disorders (1989), identified a number of research issues and problems that needed to be resolved. A subsequent NIMH research initiative, entitled Methodologic Research for Multi-Epidemiological Surveys of Mental Disorders in Child and Adolescent Populations, and conducted between 1989 and 1992, provided a solid foundation for the planning and design of the current multi-site Mental Health Service Use, Need, Outcomes, and Costs in Child and Adolescent Populations (UNO-CAP) study.

When completed, the UNO-CAP study will delineate the extent of met and unmet need for child and adolescent mental health services in the United States, the patterns of mental health service use across major service sectors, and the barriers that families experience in accessing needed services. UNO-CAP will also supply new information on socioeconomic, ethnic, family, community, and service system characteristics that affect use of mental health services, on the clinical, developmental, functional outcomes of children who do and do not receive needed care, and on the costs of care. The estimated total cost of UNO-CAP over a period of 5 years, including both the national study and the four site studies, is $45 million.

LAB TESTS

Mr. Stokes: How close are we to having effective laboratory tests for self-destructive behaviors?

Dr. Cowdry: Dr. John Mann, at the New York State Psychiatric Institute, has been a pioneer in biological studies of suicide. In a November 1994 Time article on suicide, Mann's work on serotonin and suicide was highlighted and mention was made of a possible "biological lab test" for suicide potential. Nonetheless, such a test for suicide may not be currently feasible for a number of reasons.

It is true that the most striking and consistent finding of a biological correlate of suicidal behavior is a reduction in the activity of the brain chemical serotonin. However, there is no clear way to make a biological finding into a sensitive and specific test which is an unequivocal marker of suicidal behavior, much like blood sugar levels are a marker of diabetes. Not enough is currently known about the specific parts of the brain involved in serotonin abnormalities related to depression and suicide. Newer technologies to study the brain and neurotransmitter systems may be impractical for general laboratory use. At present they serve primarily as a research function.

Furthermore, not all suicidal patients may show lowered levels of serotonin and not all people with low serotonin are at risk for suicide. The utility of a measure of low serotonin may ultimately be found as part of a comprehensive clinical evaluation of a patient, taking into account other biological measures, past illness, family history and psychosocial stressors. Dr. Mann's studies are dedicated to research on these several vulnerability factors in the overall evaluation of an individual's suicidal risk.

NOBEL LAUREATES

Mr. Stokes: Last month, the Committee had the benefit of hearing testimony from the Nation's Nobel Laureates. They indicated that neurological research offers considerable opportunity to further medical advances. To what extent is this area of research a high priority for your Institute, and how is it being used to help unravel and to increase our understanding of brain and biological response mechanism and relationship?

Dr. Cowdry: Throughout its history, NIMH has played a pioneering role in developing the foundations of contemporary neuroscience and behavioral science. Since the brain is the most inaccessible body organ to study, NIMH has played a pivotal role in developing brain imaging and other methods of studying brain function, and in using these techniques to gain a clearer picture of how the brain processes new information and creates memories. These studies also provide information about the root causes of mental illnesses and behavioral disorders, such as depression, phobias, post-traumatic stress syndrome, developmental learning disorders, and Alzheimer's disease.

By using the tools of modern molecular biology, NIMH-funded investigators have discovered a host of new neurotransmitters, receptors, and other important molecules that are involved in brain function and in the actions of psychotherapeutic drugs. Understanding how neurotransmitter systems function in the brain will greatly enhance our understanding of brain diseases and the search for effective therapies for them. Additionally, basic behavioral research is essential to the development of effective therapies for depression, panic disorders, phobias, conduct disorders, and the social dysfunction associated with schizophrenia. It is also essential in developing and demonstrating the effectiveness of specific programs to reduce the spread of HIV infection, and is helping to identify the many risk factors contributing to the increase in violence in today's society.

Mr. Stokes: How much is included in your FY 1996 budget request for neurological research? How does the FY 1996 estimate compare with 1995 and 1994?

Dr. Cowdry: In FY 1994, NIMH spent approximately $218,443,000 on neurosciences research. The Institute expects that funding for FY 1995 will be approximately $225,390,000 and $232,516,000 in FY 1996.

MINORITY HEALTH

Mr. Stokes: Please describe the Institute's efforts to ensure that the particular concerns of minorities and women have not been overlooked in research, research training, and outreach funded by the Institute.

Dr. Cowdry: The Office of the NIMH Associate Director for Special Populations, created in 1980 by the Public Health Service Act, has as part of its responsibility developing and coordinating research and administrative policies and programs to assure appropriate emphasis on the mental health concerns of women and minority populations. This Office collaborates with the NIMH research divisions to develop specific initiatives. For example, fundamental to the advancement of research on minority populations is an increase in the number of minority investigators. Cognizant of this need, NIMH's research training supports such programs as the Career Opportunities in Research Education and Training grants (COR); the Minority Institutions Research Development Program (MIRDP); and highly successful Minority Fellowship Programs (MFP) in several discrete disciplinary areas: psychiatry, psychology, nursing, social work, sociology, and neuroscience. One measure of success is seen in the MFP neuroscience programs administered under the auspices of the American Psychological Association and the Society for Neuroscience. The fellowship programs now are the country's major single contributor to the advanced training of minorities in the basic neurosciences; in 1991 alone, they graduated 9 minority Ph.D.s in the neurosciences, more than doubling the 1989 output of the entire country. In 1991, a Minority High School Science Education Program was initiated. This program consists of supplemental awards to active COR grants aimed at encouraging minority high school students to select career disciplines related to research on mental and addictive disorders. These supplemental awards provide pre-college students with hands-on experience working on research projects with faculty and COR trainees over a 2-year period. The COR program is a highly effective resource as indicated by the success of the 85 percent of trainees who go on to advanced graduate level training.

On behalf of women, the Institute has very active programs of research focusing on gender differences in specific disorders, e.g. major depression, anxiety, panic, and phobic disorders. To inform the public about this research and other initiatives the "Women's Mental Health Research Bulletin" was launched in Fall of 1994 as a semiannual newsletter. It has two main objectives: 1) to enhance the recruitment, retention, and advancement of women in research and academic careers and 2) to improve the quality of scientifically sound research applications by all investigators researching women's mental health by informing them and other interested persons about NIMH activities in women's mental health research. NIMH also supports a program for administrative supplements to research grants to support individuals with high potential to enter an active research career after taking time off to care for children or parents or to attend to other family responsibilities. Women pursuing science careers are finding this program especially helpful.

CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and have yielded comparable economic savings as well. What are the two most significant trials that are underway at the Institute?

Dr. Cowdry: NIMH focuses its funding on trials which would not be funded by private industry. This may involve early, small scale studies of drugs with novel mechanisms of action or later studies of drugs originally marketed for other indications. For example, NIMH supports studies of drugs that are already on the market to:

1) more clearly define the predictors of response for an established indication; 2) extend the application of the drug into under-researched populations (such as children and adolescents); 3) extend the application of the drug into other disorders for which it is not labelled (including rare diseases that are not "profitable," or diseases for which the manufacturer has no intention of seeking specific labelling--the use of anticonvulsants in psychiatric disorders being a prime example); and 4) explore specific biological hypotheses of drug action or effects of the drugs (including effects on brain function or receptor binding sites). Other NIMH clinical trials which would not be conducted by private industry compare drug therapy with non-drug therapy, often including a "combined therapy" arm, attempting to establish the relative efficacy of each treatment, differential predictors of response, and possible synergy between the treatments. Examples include comparisons of medication, behavioral or psychotherapies, and combined approaches in the treatment of depression, panic disorder, schizophrenia, obsessive-compulsive disorder, etc.

Significant trials now underway:

- Multisite, multimodal treatment study of attention-deficit hyperactivity disorder in childhood. This is an ongoing six site study that compares alternative treatment strategies for Attention Deficit Hyperactivity Disorder (ADHD). Subjects are assigned to one of the four possible conditions: a) an intensive, comprehensive package of psychological and behavioral treatments; b) medication using an algorithm which ensures individually tailored, optimally titrated dosing; c) the combination of both psychological and medication treatments; or d) referral to families' primary care providers for treatments determined by the providers and families.

- Clozapine (trade name: Clozaril) is a greatly improved but expensive treatment for patients with schizophrenia who have not responded adequately to standard antipsychotic drugs. A year's supply of clozapine tablets, plus the associated weekly blood monitoring that is required, costs $5,000 to $10,000 per patient. With NIMH funding, the Connecticut Department of Mental Health is conducting a randomized trial to determine cost-effectiveness of clozapine compared to usual care for 227 patients with schizophrenia in Connecticut state hospitals. Findings to date are that discharge rates associated with clozapine and usual care do not differ, but that, once discharged, patients assigned to clozapine are far less likely to be readmitted to a state hospital. Six months after discharge, 35 percent of patients in the usual care condition had been readmitted, compared to only 4 percent of patients being treated with clozapine. By the end of the two year study period, patients in the clozapine arm of the study were spending an average of 3.5 fewer days hospitalized per month than were patients in the usual care condition. This difference in hospital use, if maintained, equates to an annual savings in hospital costs of approximately $15,699 per person. While this savings is more than enough to offset the cost of the medication, further analyses being funded by NIMH will indicate whether the savings remain when costs of community mental health services used by the patients taking clozapine are compared with costs incurred for the same services by patients in the usual care condition.

Mr. Stokes: To what extent are there new clinical trials planned for implementation in FY 1996?

Dr. Cowdry: NIMH estimates that there will be approximately 29 non-AIDS competing clinical trials in FY 1996, however, it is too soon to predict what the topics of these trials might be. No new AIDS clinical trials are planned at the current time.

Mr. Stokes: What level of funding is included in the FY 1996 budget for clinical trials? How many trials would be funded? How many of these trials are new and how many are ongoing?

Dr. Cowdry: In the FY 1996 Budget Request, $56,177,000 is included to fund 175 Non-AIDS and AIDS clinical trials in all phases. Of these, 29 are new and 146 are ongoing.

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously? Is there a specific system in place for disseminating such information, explain?

Dr. Cowdry: Yes, we are doing better at getting the results of clinical trials disseminated, but not as well as we would like. We have three systems in place for disseminating research findings. The first mode is through workshops and conferences that alert researchers and research-clinicians to new findings in specific areas (e.g., domestic violence). A second mode is the NIMH Office of Scientific Information that responds to public requests for information, and has been involved in national campaigns on awareness, diagnosis and treatment of panic disorder, depression, and most recently, eating disorders. The third mode is through developing programs that enhance the exchange of information among mentally ill consumers, family members, mental health professionals, and researchers to ensure equal access to that information. For example, we are currently planning a workshop with the Substance Abuse and Mental Health Services Administration's Center for Mental Health Services in which the research findings on family involvement in the care of the severely mentally ill are shared with the community practitioner for discussion and translation into policy and treatment programs.

OPPORTUNITIES

Mr. Stokes: Please describe the three most promising opportunities in basic as well as clinical research you anticipate for your Institute in the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Cowdry: NIMH has recently surveyed current scientific opportunities and selected three areas that appear to be the most promising over the next several years. NIMH intends to emphasize studies of:

The biology of brain disorders - New and powerful technologies that make it possible to observe the living human brain have created extraordinary opportunities for learning how a healthy brain works and, most importantly, which brain biological systems are involved, and how they are involved, in specific disorders of the brain.

Other new techniques of molecular biology enable us to discover and understand the roles of specific genes in the brain, as well as precise details of the actions and importance of brain neurotransmitters and potential therapeutic agents. The knowledge derived from these basic studies will, in turn, enable clinical scientists to develop better treatments, adjust these treatments to individual patients, and observe the effects of the treatments on the patients' brain areas involved.

The genetics of complex mental disorders - Although some mental disorders appear to be transmitted through relatively simple patterns of inheritance, most mental disorders probably result from complex interactions among a variety of genetic and environmental risk factors. Recent rapid advances in molecular genetics have now provided powerful tools for identifying the multiple genes associated with complex human diseases, identifying the function of those genes, and clarifying how that biological or genetic risk then contributes to the development of widespread and costly mental illnesses. These opportunities range from fundamental research in molecular genetics, to animal models of heritable diseases and traits, to the clinical investigation of specific diseases which show complex genetic components. NIMH has already begun efforts to identify multiple genetic factors involved in schizophrenia, bipolar affective disorder (manic-depressive illness), and Alzheimer's disease. This work needs to be expanded to other psychiatric disorders, including obsessive-compulsive disorder; panic disorder; and childhood mental disorders such as autism and attention-deficit hyperactivity disorder.

Mental illnesses of children - The devastating impacts of severe mental illnesses have been well characterized in adults, but the seriousness of childhood psychiatric disorders has been less well documented and researched. Preliminary epidemiological data indicate that about 3 percent of young people between the ages of 9 and 17 may suffer from a severe mental disorder. Many more children and adolescents have other disorders which, while less severe, produce significant distress and disability and are often linked to problems such as poor school performance, suicide, aggressive and violent behaviors, and substance abuse. Opportunities now exist to understand the origins of child and adolescent mental disorders within the developmental framework of rapid shifts in neural, behavioral, and emotional organization that occur in different areas of the brain from infancy through adolescence. For example, research evidence is accumulating that schizophrenia is characterized by a disturbance of neurodevelopmental processes that take place from before birth into adolescence--long before disease onset--and that both genetic susceptibility and environmental influences play important roles in determining who suffers from this illness. Present challenging scientific opportunities range from basic studies of neurodevelopment through studies of psychological development and risk factors, the dimensions of childhood mental disorders and service needs, and problems of children of special populations, to the clinical diagnosis and treatment of childhood mental disorders.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past 5 to 10 years, explain?

Dr. Cowdry: From FY 1985 to FY 1994, the number of submitted competing applications for research project grants has increased by 45 percent. Success rates for NIMH have declined from 30.4 percent in FY 1985 to 21.0 percent in FY 1994. NIMH's success rates are estimated to be 19 percent in FY 1995 and 18 percent in FY 1996, indicating a continuing decline.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period?

Dr. Cowdry: The NIMH average cost of new and competing RPGs has increased approximately 7 percent per year over the 10 year period. Since the implementation of the Cost Management Plan (CMP) in FY 1991, however, the average increase has dropped to approximately 3 percent, close to inflation as measured by the Biomedical Research and Development Price Index (BRDPI). NIMH anticipates that the average cost of all RPGs will continue to average inflationary increases, as set forth in the CMP.

Mr. Stokes: What is the trend in terms of constant dollars?

Dr. Cowdry: In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average cost of new and competing research project grants increased by approximately 2 percent per year. Since FY 1991 and the implementation of the Cost Management Plan, the average cost decreases approximately -2 percent per year.

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Cowdry: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NIMH is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Also, on average, approximately 5 percent of grant applicants choose not to complete the portion of the grant application referring to race and gender and have been coded in the "unknown" category. There is no way to predict the race or gender composition of those applicants. Thus, the following data may not provide a true representation of NIMH's support of minority and women researchers.

The following table lists success rates for minority researchers, including a category identified as "unknown" for those grant applicants who chose not to identify their ethnic origin and/or gender. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIMH's support of minority researchers:

Competing Grant Success Rates for Minority Researchers
FY 1994
NIMH

Asian	African-American	Hispanic	Native Amer.	Unknown	White
17.7%	14.3%	8.3%	25.0%	26.0%	19.5%

Mr. Stokes: What is the success rate for research applications received from women?

Dr. Cowdry: The following data identifies success rates for women researchers who chose to answer the optional questions on the grant application related to race and gender. A category denoted as "unknown" represents success rates for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIMH's support of women researchers:

Competing Grant Success Rates for Women Researchers
FY 1994
NIMH

Female	21.7%
Male	19.0%
Unknown	44.7%

Mr. Stokes: What is the success rate for research applications received from African Americans?

Dr. Cowdry: The following data identifies success rates for researchers of African American descent who chose to answer the optional questions on the grant application related to race. A category denoted as "unknown" represents success rates for applications in which race could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIMH's support of African American researchers:

Competing Grant Success Rates for African American Researchers
FY 1994
NIMH

African Americans	14.3%
Unknown	26.0%

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Cowdry: The following data identifies success rates for Historically Black Colleges and Universities:

Competing Grant Success Rates for HBCUs
FY 1994
NIMH

HBCUs	8.0%

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to women?

Dr. Cowdry: The following data identifies the average cost of competing awards to women researchers in real and constant dollars. As stated previously, questions related to race and gender are optional on NIH grant applications. As a result, the following table identifies a gender category denoted as "unknown" which represents the average cost of competing grants for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIMH's support of women researchers:

Competing Grant Average Costs for Women Researchers
in Current and Constant Dollars
In Five year Increments FY 1985, FY 1989, and FY 1994
NIMH
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Women	$106.6	$106.6	$176.0	$145.1	$195.6	$127.9
Unknown	102.8	102.8	176.8	145.7	209.6	137.1

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to minority researchers?

Dr. Cowdry: The following data identifies the average cost of competing awards to minority researchers in real and constant dollars. As stated previously, questions related to race are optional on NIH grant applications. As a result, the following table identifies a race category denoted as "unknown" which represents the average cost of competing grants for applications in which the ethnicity of the awardee is undetermined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIMH's support of minority researchers:

Competing Grant Average Costs for Minority Researchers
in Current and Constant Dollars
In Five Year Increments FY 1985, FY 1989, and FY 1994
NIMH
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Asian	$115.4	$115.4	$204.7	$168.7	$178.1	$116.5
Black	287.9	287.9	161.3	133.0	87.6	57.3
Hispanic	51.7	51.7	125.5	103.4	195.0	127.5
N. Amer.	0.0	0.0	0.0	0.0	292.4	191.2
Unknown	102.8	102.8	168.5	138.9	241.3	157.8
White	113.7	113.7	176.8	145.7	190.8	124.8

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to African American researchers?

Dr. Cowdry: As shown in the previous table, the average costs of African American researchers in constant and current dollars are as follows:

Competing Grant Average Costs for African American Researchers
in Current and Constant Dollars
In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIMH
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Black	$287.9	$287.9	$161.3	$133.0	$87.6	$57.3
Unknown	102.8	102.8	168.5	138.9	241.3	157.8

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to HBCUs?

Dr. Cowdry: Average Costs of all awards to Historically Black Colleges and Universities in current and constant dollars are as follows:

Competing Grant Average Costs for HBCUs in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NIMH
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
HBCUs	$242.9	$242.9	$75.7	$62.4	$159.9	$104.6

ADOLESCENTS AND MENTAL HEALTH

You mention that childhood and adolescent mental health are a longstanding priority at NIMH--and that NIMH has a new initiative to obtain better data about child mental disorders and treatment.

Ms. Lowey: Could you tell us more about this initiative? Will this help us provide better treatment to children and adolescents with mental disorders?

Dr. Cowdry: In September 1994, the NIMH began funding the most important study ever undertaken in the United States on the mental health needs of children and adolescents and their use of mental health services. The study, known as the Study of Mental Health Service Use, Need, Outcomes, and Costs in Child and Adolescent Populations (UNO-CAP), will provide the first reliable national data on the mental health needs of children of different ethnicities, the types of mental health services they use, the costs of these services, and the impact of these services on children and their families. The study has two major parts. A national survey of 7,000 children and adolescents, ages 4 to 17, and their families is being conducted by investigators based at the University of Chicago. Household interviews will be conducted on an annual basis in order to generate the first reliable data on the extent, characteristics, and distribution of children's mental health problems in the Nation and associated service use. Related studies in Los Angeles (University of California at Los Angeles), Missouri (Washington University), North Carolina (Duke University), and Baltimore (Johns Hopkins University) will undertake more detailed examinations of mental health services provided to urban and rural children and adolescents across six major service sectors - education, general health care, child welfare, juvenile justice, substance abuse, and mental health. These studies will also use interviews with families and children to assess the extent of unmet need for child mental health services, ways in which organization and financing of services affects availability of services, barriers that families and children face in accessing needed services, effectiveness of mental health services when provided, and costs of these services. The research effort will take 5 years to complete. Altogether, almost 20,000 children between the ages of 4 and 17 and their families will be interviewed.

BEHAVIORAL SCIENCE

Ms. Lowey: You mention that behavioral sciences--together with neuroscience--can help us understand the risk factors contributing to the violence in today's society. What more can you tell the committee about NIMH's research in this area? What can science tell us about the violence in our society? Specifically, could you tell the committee about your research in the field of disorders that lead to child abuse and spouse abuse?

Dr. Cowdry: NIMH supports basic and applied research on the causes, characteristics, course, correlates and consequences of many types of violent interpersonal behavior, including youth violence, family violence, especially abuse of children and intimate partners, and sexual violence. NIMH support for research on violent behavior over the past 30 years has resulted in an accumulation of scientific knowledge that has informed the understanding of the nature and causes of violent behavior and its impact on those that perpetrate or are the victims of violence. This basic research has,in turn, informed the development of interventions for violent behavior, and pointed to promising directions for improvements in such interventions.

One consistent finding in violence research is that there are many variations in the types of violent behavior, the characteristics of those who engage in violent behavior, and the impact of violence on individuals. Often, the characteristics of and risk factors for violent behavior are associated with the level of severity of the violence perpetrated. Thus, research has documented that many forms of violence, such as youth violence, partner violence, and child abuse, are widespread in mild or moderate forms but that the majority of severe incidents of these types of violence are committed by a very small percentage of perpetrators. A great deal of physical abuse of children is of moderate frequency and severity and occurs in the context of harsh disciplinary practices, is often accompanied by chronic psychological abuse of the child, and is committed by parents who are experiencing economic and other personal difficulties, are socially isolated, and have poor parenting abilities. There also exists abusive situations of greater severity (e.g., repetitive beatings, burning) associated with much greater parental psychopathology and in which the child is at much higher risk for serious injury. A similar generalization can be made about spousal assaults. Physical aggression of a mild or moderate form (e.g., of slapping, pushing, or shoving) occurs relatively frequently in marital and dating relationships, may be mutual between men and women, is strongly associated with dissatisfaction with the relationship, and frequently leads to a termination of the relationship. More serious forms of physical assaults on partners are largely perpetrated by males on their partners, occur in the context of frequent psychological abuse and attempts to control the partner, frequently co-occur with sexual assaults of the partner, and are associated with serious personality disorders and frequent alcohol abuse in the perpetrator.

These research findings point to important implications for prevention efforts with victims and perpetrators of violence, namely, that different types of interventions are needed for different types of violence, especially, with respect to the level of severity of the violence. Thus, for both severe types of child and partner abuse the primary focus of intervention should be on guaranteeing the protection of the victims from the perpetrator through removal of the victim or perpetrator from the situation and/or criminal justice sanctions on the perpetrator. For the more frequent mild and moderate forms of violence perpetration, interventions should focus on:

- for child abuse reduction of stress and social isolation of parents and education on more positive parenting practices and,
- for partner abuse modification of attitudes that accept physical aggression in relationships and promotion of positive patterns of intimate interactions.

Of further relevance to violence prevention efforts is the knowledge gained from NIMH-supported research to shed light on the risk factors that lead to individuals to become violent in different settings (e.g., with children, partners, peers, or strangers). The best current risk factor models indicate that there is not any single risk factor for engagement in violence but risk factors can exist at the following levels:

- the individual biological (e.g., lowered levels of certain neural chemicals);
- the individual psychological (e.g., lower intelligence or higher impulsivity);
- the familial (e.g., experiencing or witnessing violence in one's childhood family);
- social group (e.g. peer group-support for physical aggression against women or children); and
- community (e.g, disorganized communities with high levels of community violence also tend to have higher levels of family violence).

The influence of risk factors tends to accumulate such that the higher the number of risk factors, the higher the probability of individuals becoming violent. For this reason, NIMH has supported research that is focusing on psychosocial, psychopharmacological, and community level interventions for violent behavior.

Ms. Lowey: I understand that NIMH will be producing a coordinated implementation program to address the recommendations in two reports: "The Prevention of Mental Disorders: A National Research Agenda" and "Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research." Could you tell us more about these reports -- and where you think they could lead us in our efforts to design preventive approaches to disorders?

Dr. Cowdry: The Institute of Medicine (IOM), with a 2-year contract from NIMH, established a blue ribbon committee to address a Congressionally mandated study of the status of prevention research. A report was presented to the National Advisory Mental Health Council (NAMHC) in January 1994. The NAMHC accepted the report and referred it to a committee of the Council, the NIMH Committee on Prevention Research, with instructions to develop an Implementation Plan taking into account a previous Committee on Prevention Research report. The Committee has held a number of meetings, including a National Conference on Prevention Research, to respond to the NAMHC request. The Committee will be presenting their Implementation Plan to the NAMHC on May 15. This report is an integration and summary of the conclusions and recommendations of two national scientific committees, the NIMH Prevention Research Committee, and the IOM Committee on the Prevention of Mental Disorders, all concerned with advancing the scientific agenda for research on the prevention of mental disorders.

The Implementation Plan report constitutes a national agenda for research efforts aimed at the prevention of the full spectrum of mental disorders and represents the culmination of more than five years of scientific investigation and review. The NAMHC, as an advisory group to the NIMH Director, will review and discuss the report and provide advice to the NIMH Director. The report will include recommendations on:

- scientific opportunities for prevention research in mental health;
- increasing training capacity in prevention research;
- NIMH organization and leadership for prevention of mental disorders.

BREAST CANCER AND MENTAL HEALTH

Ms. Lowey: You state in the budget justifications that breast cancer patients who strengthened their coping skills through group psychotherapy increased their survival time in comparison to those patients not in therapy. This seems to me to be very important information.Can you discuss these findings in more depth? Should we be doing more to assure that patients have greater access to such treatments and therapy?

Dr. Cowdry: NIMH considers psychosocial intervention research to be very important and continues to encourage applications in this area. An NIMH supported study conducted by Dr. Spiegel obtained evidence that patients randomly assigned to supportive group therapy showed lower mood disturbance, a 50 percent reduction in pain, and longer survival time of 18 months, than did control patients offered routine oncological care alone. This treatment involves helping patients form strong social bonds, deal directly with their fears of dying and death, restructure life priorities, improve communication with family, friends, and physicians, and control pain through training in self-hypnosis. The results of this research have been replicated in patients with lymphoma and melanoma. NIMH is now supporting a replication of this by the same investigator in which the potential psychological, psychosocial and immune system mediators of these effects on quality and quantity of life are being examined. No results from this replication are yet available because not enough time has elapsed since the beginning of the project. Dr. Spiegel has submitted a competing continuation application for the next phase which is currently under scientific review. We expect that the review will be highly favorable and if so, this project will receive every consideration for continued funding. NIMH also supports other studies of the influence of psychosocial factors on cancer patients.

The following summary of the close-out report for the NIMH grant on Prevention of Relapse in Sex Offenders was submitted for the record by Mr. Istook. The complete document is available in committee files.

FORM APPROVED
OMB NO. 68-R1452

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE OF MENTAL HEALTH

FINAL REPORT GUIDELINES

Month		Year	
0	7	9	0
(01)	(02)	(03)	(04)

INSTRUCTIONS

PHS policy requires that grantees submit a "terminal progress report" (final report) within 90 days after completion of the grant.

Please complete this series of items *as this final report.* The report will be filed with your applications, reports and other grant business in NIMH's central files. It will be read by staff in research program areas, and may be read by other Institute staff concerned with program analysis, communication, evaluation and planning. The report will be used for information about your research, i.e., to describe and summarize the information *(procedural as well as substantive)* resulting from NIMH support, and to relate that information to mental health problems and research. Your report will often be used apart from your application; however, other documents, such as publications and applications, will be available from the project file if needed.

These guidelines have been designed with relatively small response spaces to encourage brevity. However, do not restrict your response if more space is needed: be complete, using additional labeled pages inserted where necessary *(sample page included).* Extensive descriptions and discussions, if desired, should be made *in addition to* your summary response to the item, and should be placed as appendices. Discussions of issues not covered by these guidelines are also welcome as appendices. Use clear, concise language, avoiding highly technical language *where practicable (this will vary for different types of research);* appendices could be more technical than responses to the items.

All publications resulting from this project, and not previously submitted, should be submitted with this report *(or as soon as available);* see the section on Dissemination. Publications should *not* be used in lieu of responses to particular items.

Send copies of this report and all appendices as indicated below.

All Grants
Send 3 copies *

TO: Grants Closeout Unit
Grants Management Branch
Office of Program Support
National Institute of Mental Health
5600 Fishers Lane, Room 7C-[illegible] 26
Rockville, Maryland 20857

* *Send two copies only of any books included.*

FOR NIMH USE ONLY

Branch/Section: A V -
Termination Date 9·30·90

ADMINISTRATIVE DATA:

(NOTE: If items 1-4 have changed, give the latest information)

1. GRANT NUMBER

R	0	1	M	H	4	2	0	3	5
(05)	(06)	(07)	(08)	(09)	(10)	(11)	(12)	(13)	(14)

2. TITLE OF GRANT
Prevention of Relapse in Sex Offenders

3. NAME OF PRINCIPAL INVESTIGATOR
Katurah Jenkins-Hall, Ph.D.

4. SPONSORING INSTITUTION
Florida Mental Health Institute
University of South Florida

SIGNATURE OF PRINCIPAL INVESTIGATOR
Katurah Jenkins-Hall

5. NAME AND POSITION OF PERSON WRITING THIS REPORT IF OTHER THAN ITEM 3
Same as #3

ADM 442
Rev. 8-80

CONTINUE ON REVERSE SIDE

GRANT NUMBER: R01MH42035

12. Describe (a) your *conclusions or results* as they relate to your specific aims *(please include negative results)*, and (b) their *significance* in relation to the field. Avoid highly technical language where practicable.

RESULTS:

Utility of Measures in Classifying Offenders. The utility of the Slide and Audio assessments and the Sexual Activity Card Sort-Revised in classifying subjects into subgroups based on the diagnosis of male versus female pedophilia[3] at intake was tested using discriminant function analyses. The Card Sort discriminant function classified offenders with 85% accuracy ($k=.70$). The Audio Assessment discriminant function classified offenders with 80% accuracy ($k=.61$), and the Slide Assessment discriminant function classified 1qwith 87% accuracy ($k=.74$). The best classification equation was a combination of selected variables from the Card Sort, Slide and Audio Assessment (89%, $k=.78$) however, this combination did not improve classification power significantly. (Laws, Greenbaum, Osborn, & Murrin, in preparation).

Differential effects of the two treatment packages, RET/BT + RP (E) vs. RET + CF (C). To test the differences between treatment packages, repeated measures mixed model ANOVAs were conducted comparing all scores on **between phase measures** across treatment phases as follows: Baseline through the end of Phase 1 (0-1), Baseline through the end of Phase 2 (0-2) and Baseline to the end of Phase 3 (O-3). Each analysis eliminated those subjects for whom there were missing data. Therefore the sample size in each analysis differed. In some analyses, the Experimental group is divided into type of behavior therapy received, OA or VS. Planned comparisons were conducted using Fisher's Least Significant Difference (LSD) test.

The analyses attempted to answer two major questions: 1) Do groups change across phases and 2) Are there group differences in the rate or type of change? More specifically, do Es fare better than Cs? Prior to between phase analyses, pretreatment differences between Es and Cs were analyzed. Physiological data were analyzed using both relative (i.e., ratio) measures for deviant and nondeviant arousal and raw percentage scores. **Relative arousal** (i.e., Deviant /Deviant + Nondeviant) was used at the recommendation of the Scientific Advisory Board to adjust for three potential problems: (a) calibration errors in percentage scores, (b) low levels of response and (c) pretreatment differences between groups. In each case, the Nondeviant score in the ratio was the client's score on the first adult arousal baseline taken during melasurement sessions. This score was selected because it was the highest and most stable nondeviant score. The values presented in this section are relative arousal scores unless otherwise specified. The relative arousal scores are interpreted the same as percentage scores.

BETWEEN-PHASE MEASURES

1. Pedophile Slide Assessment. For the purpose of analysis, the slides were divided into two types: type 1 = children, ages 0-17; and type 2 = adults, age 25 and older. Mean responses to type 1 and type 2 slides were obtained for each subject. A two-way ANOVA revealed pretreatment differences in relative arousal for this measure as indicated by a significant Type X Group interaction ($F(2, 66) = 4.87$, $p < .05$). Groups C and VS did not differ from each other but were significantly greater than OA on responses to adult slides (Means = .49, .47, and .41, respectively (LSD = .06). Additionally, groups were not significantly different at baseline on responses to children (Means = .45, .46, and .47 for groups C, VS, and OA respectively).

The results of the repeated measures analysis of relative arousal to Slides showed no group differences across phases 0-3 despite of the pre-treatment differences noted above. The results of the analysis revealed a significant Type X Phase interaction ($F(3,111) = 5.20$, $p < .01$) indicating a decrease in deviant arousal from 0-1, and a leveling off at 2 and 3, while nondeviant arousal did not differ significantly throughout. (Means for deviant arousal for phases 0-3 = .44, .37, .34, and .36, respectively. Means for adult arousal for phases 0-3 = .44, .45, .42, and .45, respectively.)

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[3] The diagnosis of pedophilia is based on history reported by the client at intake and does not necessarily conform to DSM-III-R criteria.

GRANT NUMBER: R 0 1 M H 4 2 0 3 5

RESULTS
(Continued)

13. Did you have *other findings* not directly related to the specific aims *("serendipitous findings")?*
If yes, describe:

1 ☒ Yes
2 ☐ No (23)

(See continuation page, item no. 13.)

14. How do the *overall results* of your project fit into these descriptions?
(If you had multiple expectations or hypotheses, base your response on the predominant trend of the results).

☐ Confirming your hypotheses or expectations (24)
☐ Disproving your hypotheses or expectations (25)
☒ Inconclusive (26)

Although the predominant trend of the results indicates that RET/BT + RP may be a better treatment package than RET + CF, the results are inconclusive because of the insensitivity of certain outcome measures in detecting treatment effects, the low number of subjects and an inadequate period of follow-up to track recidivism.

15. Did your research result in significant *methodological developments?*
If yes, describe:

1 ☒ Yes
2 ☐ No (27)

(See continuation page, item no. 15.)

FINAL REPORT GUIDELINES CONTINUATION PAGE	GRANT NUMBER R01MH42035

Item No. 7

Original Aims of Project.

The original aims of the project were based on a different research design (see Figure 2). The original design, approved in 1985, compared RET/BT, Stress Inoculation Training (SIT) and RP, (the current Experimental group minus SIT), with a comparison group based on a model of short-term interpersonal psychotherapy (IPT) that had been used in the treatment of depression (Klerman, Weissman, Rounsaville, & Chevron 1984). Thus, the aim was to compare a package of cognitive/behavioral approaches to a more traditional interpersonal therapy approach. The use of the short-term interpersonal psychotherapy comparison group proved untenable, because of flaws in the treatment manual. Therefore, the original design was abandoned and the present design implemented in 1/87 as a compromise. The change occurred at the recommendation of the project's Scientific Advisory Board and was approved by the National Institute of Mental Health (NIMH) project officer. The confounds in the present design were taken into account in the 1986 review by the IRG which noted that "...[the confound] was not a very serious limitation" (NIMH, IRG Review, Grant #MH42035, 1986).

Item No. 9, page 1

Clients were randomly assigned to groups based on their date of admission. That is, the first six clients were assigned to the Experimental group, the next six to the Comparison group, etc. A coin-flip determined the selection of the Experimental group as the first group assignment. Occasionally, more or less than six clients were assigned to a group depending on the referral rate. For example, if referrals were low, a group of five might be started to avoid keeping current clients on a waiting list, or a group of eight might be started if referrals were higher but not enough to form two new groups.

Subjects

The design called for 120 male child molesters who met the following criteria: (1) aged 18-70, (2) at least low average intelligence, (3) ability to read and write at the 4th grade level, (4) English speaking, (5) non-psychotic, and (6) admission of sexual or pre-sexual interest or behavior with a child. Incest offenders were included if they had also molested outside the home.

A total of 109 clients were accepted as subjects for this study. Subjects were artificially divided into two groups, Treated ($\geq$ 10 weeks of therapy, $n=70$) and Untreated ($<$10 weeks of therapy, $n=39$). The results discussed in this report are based on data analyses of the treated group.

The treated group had a mean age of 38.73, and completed 12.61 years of education. The racial composition of the sample was 90% white, 8% black, and 2% hispanic. Thirty-six percent (36%) were never married, 34% were married or living with a partner, and 30% were divorced, separated, or widowed. About 33% earned less than $5,000 in annual income, 29% earned between $5,000 and $10,000 and the remaining 37% earned more than $10,000 per year.

With respect to clinical profiles, 83% were pedophiles (sexual fantasy about contact or actual contact with a child); 17% had other paraphilias involving children (exhibitionism, voyeurism, frottage, etc.). Sixty-six percent (66%) had female victims, 26% had male victims, and 8 % had both male and female victims. Eleven per cent (11%) had never been arrested, 64% had one arrest and 24% had two or more arrests for sex offenses. Only 23% had histories of alcoholism and 25% used alcohol during the offense. Only 20% had histories of drug abuse, and only 13% were under the influence of drugs at the time of the offense.

Chi-square statistics and one-way ANOVAs were conducted to test the differences between the Treated and Untreated groups. The following is a summary of the results that were obtained:

1) Age. Treated clients were older than Untreated clients, Mean ages = 38.73 and 33.21, respectively ($F(1.108) = 5.10$, $p<.05$).

2) Education. Treated clients completed more years of education than Untreated clients, mean number of completed grades = 12.61 and 11.12 respectively ($F(1.108) = 6.57$, $p<.05$).

3) Race. While the vast majority of clients were white, blacks were equally represented in treated and untreated groups but hispanics were underrepresented in the treated group ($X^2 = 7.39$, $p<.05$).

4) History of alcohol problems. The treated group was less likely to have a history of alcohol problems than the Untreated group ($X^2 = 6.69$, $p<.01$).

5) Use of drugs during offense. The treated group was less likely to have used drugs during their offense(s) ($X^2 = 2.73$, $p<.05$).

The treated and untreated clients were equivalent on all other demographic variables. A more detailed description of these results can be found in Appendix B.

Chi-square statistics and one-way ANOVAs were also conducted to test the differences between the Experimental and Comparison groups among the treated clients. Results revealed that groups were equivalent on all demographic variables with the exception of sex of primary target (victim). Significantly more subjects with male victims were found in the E group compared to the C group (Chi-square=7.30, $p<.05$).

Additionally, IQ estimates were obtained for subjects based on the two-subtest short-form of the Wescheler Adult Intelligence Scale Revised (Silverstein, 1984). This estimate used the subscale score for Vocabulary as the Verbal IQ estimate and Block Design as the Performance IQ estimate. An estimated Full scale IQ score was obtained by summing the above. Independent T-tests revealed no differences between groups in estimated IQs ($t = -1.51$, E=108.84 and C=102.71). Both scores fall within the average range of intellectual functioning.

MEASURES:

For the purpose of this report, measures have been classified into four groups: Baseline measures, (administered pretreatment only), between-phase measures (administered pre-treatment and after each phase), within phase measures (administered at baseline and at weekly/ monthly intervals throughout treatment), and treatment outcome and other measures.

Baseline Measures

1. Comprehensive Intake Interview (Osborn & Jenkins-Hall, 1986, see Appendix C-1). This is an extensive five-part questionnaire consisting of 284 items. Included were questions regarding the subject's sexual history (both deviant and nondeviant), family background, educational/vocational history, and psychological/ social adjustment.

2. Multiphasic Sex Inventory (MSI) (Nichols & Molinder, 1984, see Appendix C-2). The MSI is a 300-item instrument designed to assess a wide range of psychosexual characteristics of the sex offender. There are four paraphilia scales: (a) Child Molestation, (b) Rape, (c) Exhibitionism, and (d) Atypical Sexual Outlet (Fetish, Obscene Phone Calls, Voyeurism, Bondage/Discipline, and Sado-Masochism). There are seven validity scales: (a) Justifications, (b) Cognitive Distortions, (c) Social/Sexual Desirability, (d) Sexual Obsessions, (e) Treatment Attitudes, (f) Parallel Items, and (g) Lie Scale. There is also a Sexual Dysfunction scale and a Sex Knowledge Beliefs scale. Each item is marked either true or false. Total items endorsed/total items scored are given for each scale. The complete instrument was given at Baseline and an abbreviated version was piloted as a repeated measure for subjects entering the project after 3/88 (Laws, 1988a). The modified version consisted of 31 true/false questions from the Pedophilia and Paraphilia scales. The results of the MSI are not reported due to inadequate sample size.

3. Abel/Becker Adult Cognition Scale (Abel & Becker, 1984, see Appendix C-3). This instrument measures the extent of deviant cognitions endorsed by the client. The client rates his level of agreement to various statements about sexually deviant thoughts or behaviors with children. The client answers these questions under two different instructional sets. The first asks the client to rate his agreement with the statements as he feels now. The second asks the client to rate his agreement with the statements as he would have felt before his sexual deviance was discovered. Each item is rated on a 5-point Likert scale, 1 (strongly agree) to 5 (strongly disagree). Mean scores were determined for each instructional set. This scale was originally designed to be used as a repeated measure, but was discontinued because of a ceiling effect resulting from the transparency of the items (Subjects responded in the socially desirable direction).

Item No. 9, page 3

Between-Phase Measures

Psychophysiogical measures. Procedures for the psychophysiological measurement techniques followed a pre-written manual (Osborn[2] & Murrin, 1986, Appendix D). Sexual arousal data obtained via the following techniques were analyzed using relative (i.e., ratio) measures for deviant and nondeviant arousal and raw percentage scores.

1. Pedophile Slide Assessment (Laws & Osborn, 1983). The slide assessment is composed of 36 slides, 18 per sex, divided into six categories based on criterion levels of sexual maturation (Category 0: ages 0-4; Category 1: ages 5-7; Category 2: ages 8-11; Category 3: ages 12-14; Category 4: ages 15-17; and Category 5: ages 25 and older). There are three slides per category, each presented for 2 minutes. Peak values per presentation were obtained, and category means were computed and expressed as average percentage of full erection.

2. Pedophile Audiotape Assessment (Avery-Clark & Laws, 1984; Laws, 1985). There are seven categories of audiotapes: (a) fondling a consenting child (F), (b) mutually consenting intercourse with a child (MC), (c) non-consenting intercourse with a child (NC), (d) rape of a child (R), (e) sadistic sexual assault of a child (S), (f) non-sexual physical assault of a child (PA), and (g) consenting adult intercourse (CA). There are a hetero- and homosexual series, one three minute tape per category. Peak values per presentation were obtained and expressed as average percentage of full erection.

Client questionnaires. Most client questionnaires were computerized and entered directly into the data bank by the client under staff supervision.

1. Sexual Activities Card Sort - Revised (Abel, 1979; Laws, 1986a, see Appendix C-4). This instrument is a self-report inventory of sexual interest. There are 13 scales of 10 items each, describing some variety of sexual behavior: (a) Adult Heterosexuality, (b) Adult Homosexuality, (c) Female Pedophilia, (d) Male Pedophilia, (e) Female Incest, (f) Male Incest, (g) Adult Female Rape, (h) Transvestism; and minor paraphilias with both male and female children as targets (five items each), (i) Voyeurism, (j) Exhibitionism, (k) Rape, (l) Frottage, and (m) Sadism. Each item was rated on a 7-point Likert-type scale, 1 (Very Attractive) to 7 (Very Unattractive).

2. Symptom Checklist-90 (SCL-90) (Derogatis, Lipman & Covi, 1973, see Appendix C-5). The SCL-90 is a 90-item self-rating scale used to screen for evidence of pathology. The checklist has nine clinical symptom dimensions: (a) Somatization, (b) Obsessive-Compulsive, (c) Phobic Anxiety, (d) Paranoid Ideation, (e) Psychoticism, (f) Interpersonal Sensitivity, (g) Depression, (h) Anxiety, and (i) Anger-Hostility. Items are rated on a 5-point Likert scale, 0 (not at all) to 4 (quite a bit). A mean score for each dimension was determined. For the purpose of these analyses four scales (f-i) were of interest as they were expected to reflect changes resulting from RET treatment interventions which focused specifically on these clinical areas.

3. Self-Efficacy Scales (Laws, 1986b; Marlatt, 1985, see Appendix C-6). These scales assess the degree that clients believe they will be successful in particular situations and what their outcome expectancies are. This instrument is divided into three (3) scales which the client is asked to rate how he would behave in twelve (12) different situations, e.g. "finding

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[2] C. Osborn was the behavior laboratory coordinator and project administrator of CPCM.

Item No. 9, page 4

yourself in the company of children." The first scale asks the client how often he experiences the twelve situations. The second scale asks the client how tempted he would be to molest children in those situations and the third scale asks the client how confident he is that he could resist the temptation to molest children in those situations. Each item is rated on a 7-point Likert scale, 1 (not in past year/not tempted/not at all) to 7 (at least once daily/extremely tempted/extremely confident). A total score was determined for each of the scales.

4. Global Improvement Rating Scale (Luborsky, 1975, see Appendix C-7). This is a single dimension, 9-point Likert scale used by the client to evaluate his progress across each treatment phase, from 1 (worse) to 9 (outstanding, great improvement).

Therapist questionnaires. Therapists also entered their responses to these questionnaires directly into the data bank.

1. Brief Hopkins Psychiatric Rating Scale (Derogatis, 1978, see Appendix C-8). This scale is similar to the SCL-90 except that symptom dimensions are rated by the therapist. The scale has nine dimensions: (a) Somatization, (b) Obsessive-Compulsive, (c) Phobic Anxiety, (d) Paranoid Ideation, (e) Psychoticism, (f) Interpersonal Sensitivity, (g) Depression, (h) Anxiety, and (i) Hostility. Items are rated on a 7-point Likert scale from 0 (none) to 6 (extreme). The same four scales as the SCL-90 (f-i) were also used for this analysis.

2. Global Improvement Rating Scale (Luborsky, 1975, see Appendix C-7). This is the same 9-point scale described above.

3. Outcome of Therapy (Storrow, 1960, see Appendix C-9). This instrument is used by the therapist to rate clients' current level of functioning on various therapy outcome dimensions. There are three primary dimensions to this instrument: (a) Symptoms or Problems, (b) Interpersonal Relationships, and (c) Ability to Handle Stress. These primary dimensions are subdivided into individual traits. Each item is rated on a 5-point Likert scale, 1 (much worse) to 5 (much better).

4. Predictor Scale (Laws, 1986c, see Appendix C-10). This instrument was used to evaluate clients on various factors felt to be predictive of potential relapse and included both historical and current factors,(e.g. history of alcohol abuse, total number of victims, percent of current deviant masturbatory fantasies, etc.). The scale consists of 22 multiple-choice items. This scale was completed at Baseline and Termination only.

5. Significant Other Rating Scale (SORS) (Jenkins-Hall, 1987a, see Appendix C-11). This instrument was piloted in this study. It is completed by a significant other identified by the client as being knowledgeable of his daily activities. Significant others rate the frequency of deviant behaviors engaged in by the client as well as various indicators of lifestyle adjustment (e.g., "participated in a social activity with a non-relative child, behaved secretly, appeared sad, made spur of the moment decisions"). Items are rated on an eight-point Likert scale, from 1 (never) to 8 (more than once a day). Total scores were determined. This questionnaire, was mailed to the raters at Baseline and subsequent reassessment phases.

Item No. 9, page 5

Within-Phase Measures

Psychophysiological measures.

1. Measurement Sessions (Laws & Osborn, 1983, see Appendix D). To index progress in therapy, the original design included biweekly measurement sessions in which clients' arousal to deviant and nondeviant stimuli was measured. Measurement sessions were later changed to monthly rather than biweekly (See question #10). During measurement sessions, sexual arousal was measured while the client listened to four, three minute audiotaped descriptions of "consenting" deviant and nondeviant sexual activity with their preferred gender target presented in random order. These audiotapes are similar to the Pedophile Audiotape Assessment stimuli.

Client questionnaires.

1. Client Goal Attainment Scales (CGAS, see Appendix C-12). Goal attainment scales were designed by project staff to measure progress toward goals specific to each type of therapy. There are three types: RET (16 questions), RP (5 questions), and CF (8 questions). Items on the RET goal attainment scale are rated on a 7-point Likert scale, from 1 (not at all) to 7 (extremely well). Items on the RP goal attainment scale are rated on a 5-point Likert scale, 1 (poor mastery/infrequent use) to 5 (excellent mastery/frequent use). Items on the CF goal attainment scale are rated on 7 point Likert scale, according to the extent to which clients apply principles of RET where 1 = not at all and 7 = extremely well. The clients rated their progress in therapy on the appropriate scale on a weekly basis throughout each phase of therapy. Total scores were calculated for each week.

2. Daily Self-Reports (Laws, 1985) (DSRs, see Appendix C-13). Clients record daily frequencies of deviant and nondeviant (a) fantasies, (b) masturbations, and (c) sexual acts. They also rate their mood state on two dimensions, sad-happy and angry-calm, as well as how they define themselves on a deviant-nondeviant scale. These three scales are rated on a seven-point Likert scale. In Phases 2 and 3, they also recorded either high-risk situations (E), or behaviors short-of relapse (C). Clients completed the DSR on a daily basis and turned them in at weekly group sessions. Means for each of the dimensions for the week ending the day before measurement sessions were calculated and incorporated into the data analyses. Thus, five weekly means were obtained from Phase 1, five from Phase 2, and six weekly means were obtained for each half of the extended follow-up phase (Phases 3 and 4).

Therapist questionnaires.

1. Therapist Goal Attainment Scales (TGAS, see Appendix C-14). These instruments are the same ones described above, phrased in more technical language. The therapists also rated clients' progress in therapy on a weekly basis. Total scores were calculated for each week.

Post-Treatment Measures

1. Proficiency Tests (Laws & Jenkins-Hall, 1989, see Appendix C-15). Content related tests were developed for Rational-Emotive Therapy and Relapse Prevention. These tests consist of questions which measure the clients' mastery of the principles and concepts from each of the therapies. The RET and RP proficiency tests (20 questions each) consist of multiple-choice and fill-in-the-blank questions. These tests were administered at Termination and additionally served as a measure of treatment integrity; that is, to ensure that clients not assigned to RP were not inadvertently exposed to RP concepts by the therapists. A total score was determined for each test.

2. Situational Competency Test (SCT) (Miner, Day & Nafpaktitis, 1987, see Appendix C-16). This is a test of client coping skills in contrived situations developed at the California Sex Offender Treatment Project. Clients are videotaped as they describe how they would handle 14 proposed high risk situations, e.g. "A young neighbor girl tells you she thinks you are sexy. What do you do?" There are three versions of this test, one each for heterosexual pedophiles, homosexual pedophiles, and mixed pedophiles. These videotaped segments were scored across 10 dimensions including: the relevancy of the response, use of assertive behavior, use of avoidance or escape, and the effectiveness of the response, etc. Scaled scores for each of the 10 dimensions and a total score was determined for each client.

3. Client Satisfaction Scale (Laws, 1988b, see Appendix C-17). A client satisfaction scale was developed near the end of the project to evaluate the clients' perception of the efficacy of various components of the treatment program. This scale consisted of 8 questions rated on a 5-point Likert scale, from 1 (not important/not at all) to 5 (extremely important/definitely).

4. Client Follow-up Questionnaire (Jenkins-Hall & Osborn, 1990, see Appendix C-18). This questionnaire was designed to collect preliminary recidivism data on CPCM clients. There are 10 questions designed to elicit information on the total number of investigations, arrests, and/or convictions for each client since treatment termination. A global measure of community adjustment was also obtained and was rated on a 5-point Likert scale (1 = poor, 5 = excellent).

Apparatus

Sexual arousal was measured in a behavior laboratory using a mercury in rubber penile strain gauge or transducer. The Farrall CAT-200 computer system was used to operate the presentation of stimuli and to summarize the data. Other audio and video equipment was used for presentation and/or monitoring of stimuli. (For a complete description of the apparatus and stimulus materials used, see Appendixes D and E.)

Treatment Methods

Group Therapies. Each of the group therapies employed in this project followed pre-written treatment manuals which clearly specified the content of each group session. (see Appendix F (RET), Appendix G (RP), and Appendix H (CF) for the treatment manuals used by this project.)

Rational-Emotive Therapy (RET). (Ellis & Grieger, 1977; Lange, 1986). The premise of RET is that dysfunctional emotional states (excessive anger, depression, guilt, and anxiety) and their consequent behaviors are the result of cognitive errors in perceptions of people and events. Deviant sexual behavior is an "irrational behavior" based on an irrational belief system (cognitive distortions) used to justify the behavior.

The purpose of RET was to teach clients a set of cognitive strategies: (a) to challenge and restructure justifications used to maintain sexual deviancy, (b) to cope with anxiety, depression, guilt and anger that may precipitate sexual offending, and (c) to develop communication and assertion skills necessary for successful adult relationships. The RET component of therapy was implemented for 20 consecutive weeks for all subjects. Each session lasted 1.5 hours for Es and 2 hours for Cs. The time difference was designed to balance the additional time Es spent in behavior therapy (see Appendix F).

Item No. 9, page 7

Relapse Prevention (RP). (George & Marlatt, 1986; Jenkins-Hall & Anderson, 1987; Marlatt, 1979; 1985; Marlatt & Gordon, 1980). RP is a self-management program employed in this project as a follow-up therapy. The original procedures as outlined by George and Marlatt (1986) included didactic instructions for five group therapy sessions and 6 individual follow-up sessions. A revised manual was developed (Jenkins-Hall & Anderson, 1987) to organize the material for presentation into the 20 week format presented in Appendix G.

Clients assigned to the experimental group participated in RP during the second phase of treatment. The clients learned to identify cognitive and behavioral precursors to reoffending and to intervene at the earliest possible point in their cognitive/behavioral chains (George & Marlatt, 1986; Jenkins-Hall, Osborn, Anderson, Anderson, & Shockley-Smith, 1989). Emphasis was placed on developing skills to control deviant urges, fantasies and behaviors.

Conventional Follow-Up (CF). (Jenkins-Hall, 1987b). While subjects assigned to E participated in RP in Phase 2, subjects assigned to C participated in CF. This treatment was similar to traditional psychotherapy groups but maintained the RET emphasis. It focused upon maintenance of four basic skills learned in RET. These were the ability to (a) distinguish between irrational, rationalizing, and rational thinking, (b) identify underlying irrational beliefs that lead to excessive feelings of anxiety, depression, anger, and guilt, (c) use the four-step process of cognitive restructuring for changing irrational thinking, and (d) engage in assertive behaviors in all aspects of daily living. In addition, several sessions were designed to focus on successful community adjustment. (see Appendix H.)

Behavior Therapies. Three types of behavior therapy for reducing deviant arousal initially were considered for clients assigned to the experimental group: Olfactory Aversion (OA) (Laws, Meyer, & Holmen, 1978), Verbal Satiation (VS) (Laws & Osborn, 1983), and Orgasmic Reconditioning (Conrad & Wincze, 1976). (Orgasmic Reconditioning was not used due to concern for possible health risks associated with disposal of ejaculate.) All experimental clients either received Olfactory Aversion or Verbal Satiation. In both procedures, each week the clients performed two sessions at home, recording sexual fantasies on audiotape, and one session in the clinic. Both of the therapies followed a pre-written manual which delineated the procedures to be followed (Osborn & Murrin, 1986). The procedures are briefly described below.

Olfactory Aversion (Laws, et al, 1978; Maletzsky, 1973, 1974, 1980). The theory behind Olfactory Aversion is that if a noxious chemical agent (in this case, spirits of ammonia) is continuously paired with the presentation of deviant sexual stimuli, deviant arousal elicited by such stimuli will decrease. In this procedure, the client inhaled ammonia fumes while engaging in free deviant fantasy. Erection responses were monitored during clinic sessions. Each OA session was 15 minutes in duration and was performed at the rate of 3 times weekly, beginning in Phase 1 and continuing until the client reached the criterion of 8 consecutive weeks with deviant arousal $\leq$ 20% of full erection (FE).

Verbal Satiation (Laws & Osborn, 1983). The theory behind Verbal Satiation is that continual performance of a behavior in the same stimulus situation will lead to the extinction of that behavior. In this procedure the client simply recited deviant sexual fantasies nonstop for 30 minutes, three times per week. Theoretically, the deviant sexual fantasies would ultimately lose their power to elicit sexual arousal. This procedure also was initiated during Phase 1 and continued until the client reached the criterion of 8 consecutive weeks with deviant arousal $\leq$ 20% FE.

Item No. 9, page 8

Treatment Integrity

Group Therapy. To assess the degree to which therapists perform group therapy as prescribed by the treatment manuals, treatment integrity rating scales were developed (see Appendix C-19). The scales were comprised of items reflective of the treatment goals for a given session, and included a global integrity rating which reflected how well the therapist implemented the treatment approach in general. Scores ranged from 1-9, where 9 indicated the highest degree of integrity. Videotaped samples of each therapist's performance were obtained periodically. These samples were mailed to expert raters for evaluation (A. Lange, Ed.D., author of the RET manual, W.H. George, Ph.D., co-author of the RP manual, and K. Jenkins-Hall, Ph.D., author of CF manual). For purposes of clinical supervision, the Clinical Director also reviewed videotaped or audiotaped samples of all sessions. After reviewing 5 sessions per therapist and providing them with feedback, the average integrity rating for RET was 7.1, the average rating of RET/BT was 6.9, the average rating for RP was 8.0 and the average rating for CF was 7.5. A score of 7 was considered to be the acceptable target level. The process of having external expert raters proved to be inefficient and was therefore discontinued after the first year of operation.

Behavior Therapy. The treatment sessions in the lab were closely monitored. If a client deviated from the treatment protocol as specified in the Behavior Therapy Manual (see Appendix D), the entire session was repeated. Homework sessions were reviewed and feedback regarding compliance was given to clients on a weekly basis. In addition, a compliance index scale was developed (Osborn & Laws, 1988, see Appendix C-20) to quantify the clients' level of compliance with each session. The scales ranged from 1-5, where 5 represented the highest level of compliance. A score of 4 was considered to be the target level. Clients received an average compliance index of 3.62 and 3.66 for lab sessions during Phases 1 and 2, respectively; and 2.97 and 2.86 for homework sessions during Phases 1 and 2, respectively.

FINAL REPORT GUIDELINES CONTINUATION PAGE	GRANT NUMBER R 0 1 M H 4 2 0 3 5

Item No. 10, page 1

Technical Methodological Difficulties.

1. Confounding in the present design. Figure 1 shows that the design was indeed confounded. The differential impact of relapse prevention (RP) and conventional follow-up (CF) could not be independently determined because each does not follow the two treatments offered: RET/BT and RET. Because of the limitations of the design, the present study can only compare two packages of treatment with each other.

2. Compromised selection criteria. The project began with the intention of recruiting clients who met the DSM III-R diagnostic criteria for pedophilia. The rationale was to select those individuals upon whom the treatments were most likely to impact. A low referral rate indicated that these criteria were unrealistic and they had to be broadened. Thus it proved necessary to widen the age range, lower the intelligence requirement (IQ >80), and accept individuals who engaged in sexual and pre-sexual activities with children but did not necessarily meet the DSM III-R criteria for pedophilia, e.g., exhibitionists with pedophilic tendencies. Thus, entry criteria were adjusted to match those used by most outpatient community programs.

3. Inadequate subject pool. The rate of referral to the project was significantly underestimated. The project did not anticipate the effect that a competing community sex offender program would have on referrals. Probation officers, already familiar with the services of the competing program, required time and attention to be persuaded to try another avenue of treatment. The fact the project was known as "experimental" also made community referral agents hesitant to trust the program with its sex offenders. Although referrals were steady, from 10-12 a month, the protocol called for twice that rate (see Appendix I). To boost the rate of referrals, extensive mailings were made to potential referral sources, in-service training events were held to which key sources were invited, and several community presentations to Florida Probation and Parole officers were made.

4. Reactivity of measurement. In 05/88, during a site visit from NIMH and the project's Scientific Advisory Board, it was concluded that psychophysiological measurements occurred too frequently and that the lack of results observed to that point (11/87) could be a result of the reactive effect of measurement. This was echoed in the Evaluation Summary (08/88). Immediately following the site visit, measurement sessions were changed from biweekly to monthly.

5. Sensitivity of measures in detecting treatment effects. This project used many of the same instruments (e.g., Multiphasic Sex Inventory (MSI), and the Abel-Becker Cognition Scale) to measure treatment outcome as other major sex offender research projects. However, preliminary results revealed that these measures were not sensitive to detecting treatment effects. Consequently, in 1987 the project began to thin out measures, dropping those instruments that were not performing from the research procedures. In addition, two tests were added to evaluate the extent to which clients had learned the concepts presented in treatment: the Situational Competency Test and RET and RP proficiency tests.

FINAL REPORT GUIDELINES CONTINUATION PAGE	GRANT NUMBER R01MH42035

Item No. 10 , page 2

6. Nonresponders. Because of the low rate of referral, this project did not screen our clients who were nonresponders to psychophysiological assessment (i.e., <20% FE to all sexual stimuli). Data from nonresponders lowered the mean level of responsiveness and reduced the potential for the level of change in arousal needed to detect treatment effects (i.e., data was subject to floor effects). Random assignment distributed nonresponders across groups, and therefore floor effects should have been randomly distributed. The Scientific Advisory Board also questioned whether nonresponders should receive BT. There is no evidence that clients with minimum or no arousal do not benefit from BT. In fact, many child molesters respond emotionally to sexually deviant stimuli, even when physical responsitivity is undetected.

7. Compromised random assignment. The IRG objected to the fact that clients were randomized in "bunches" rather than alternately assigned to one or the other treatment as they came in the door. The grouping was necessitated by the nature of the treatments and the low rate of referral. Treatments were conducted in "closed" rather than "open" groups. Treatments were administered in 20 week blocks, each session conducted according to specifications in a treatment manual, and clients had to begin treatment at the first session. In order to truly randomize incoming clients, it would have been necessary to individually tutor latecomers, then insert them in an ongoing group. Sufficient staff were not available to do this, and such a procedure would have negated the benefit of group process. The other alternative was to place clients "on hold" until enough had been referred for random assignment. This also was logistically problematic due to insufficient staff and space to start several groups at the same time and was considered ethically untenable.

FINAL REPORT GUIDELINES CONTINUATION PAGE | GRANT NUMBER R 0 1 M H 4 2 0 3 5

Item No. 11

Operational Difficulties.

Year 01 of the research project started on 1/15/86. Immediately after the start-up, word of the nature of the research reached the local press and spread statewide. The press stated that the project would be using its federal certificate of confidentiality to conceal known sexual crimes and violate the state reporting statutes. It was also alleged that known sex offenders were deliberately being exposed to child pornography, and then set loose on the community. These issues attracted the attention of the Church Of Scientology who began a nationwide campaign of letter writing to local, state, and federal officials; radio and TV appearances; and picketing in order to terminate the research project. As a consequence of these attacks, NIMH ordered a review of all informed consents to fully clarify program procedures, and to cover procedures for dealing with all possibilities of client misconduct. Consent forms were modified (as they appear in Appendix A) and the attacks by the Church Of Scientology were systematically countered by the project director. These attacks eventually subsided.

Additionally, the manual for a major component of treatment (Short-term Interpersonal Treatment) was discovered to be flawed and the research design had to be changed during the first year (See question # 7). Because of the start-up problems, clients were not officially accepted in the program until 1/87.

Once clients entered treatment, aspects of the research design and practical clinical concerns contributed to a loss of sample data. First, admission to the groups was closed after the beginning of the first RET session. This was necessary because of the structured nature of each treatment session, which built upon knowledge of previous sessions. Therefore, when attrition occurred, groups that may have started with 7-8 members sometimes finished with 3-4 members. This was, of course, cost-ineffective with respect to the staff time needed to conduct the sessions.

Attrition could occur for a number of reasons (e.g., some subjects moved out of the catchment area, while others were incarcerated for violation of probation orders). Attrition rates and reasons for termination are discussed in Appendix J. In addition to the above reasons, subjects were sometimes terminated because of non-compliance with the treatment protocol. Inherent in the protocol were very stringent compliance requirements regarding session attendance, completion of homework assignment, and quality of participation in treatment (These are outlined in the CPCM Client Handbook, see Appendix K.) So, not only was sample size compromised at the hands of the clients, but also because of strict program rules.

Perhaps the most critical operational difficulty came at the beginning of year 04, when the original Principal Investigator resigned his position, necessitating a change in PIs. As a result of this resignation, and the subsequent change in PIs, new admissions were halted in 3/89, resulting in a less than desirable number of subjects upon which to base future studies. This resignation also placed the project's year 04 funding on hold. In 4/89, a new PI was appointed (formerly the co-PI and Clinical Director), and funding was reinstated for an orderly termination of the project.

Item No. 12, page 1

In summary, although C and VS started with higher arousal to adult slides than OA, there were no significant group differences on child or adult slides across phases 0-3. For all groups, deviant arousal decreased sharply from 0-1 and leveled off at 2 and 3. Adult arousal did not change significantly from 0-3.

2. Pedophile Audiotape Assessment. Relative arousal to audio assessment was analyzed by grouping tapes into four types: (a) consenting adult, (b) no violence (F&MC), (c) moderate violence(NC&R), and (d) extreme violence(S&PA). There were no pretreatment differences between Es and Cs on this measure. Across 0-3, results of the repeated measures ANOVA revealed a significant main effect for Phase (F(3,108) =8.84, p<.001), with relative arousal decreasing across phases (means = .50, .42, .40, and .41, with significant differences between 0-1 only. There was a significant linear trend (F(1,36)=16.36, p<.001) and significant quadratic trend (F(1,36)=4.83), p<.05) indicating that arousal decreased sharply from Baseline through Phase 1. Additionally, there was a significant Type effect, (F(3,108)= 15.67, p<.001, means = .49, .46, .42, .36) with a significant linear trend F(1,36)=28.14, p<.001, indicating a significant decrease in arousal to stimuli as violence increased. There was also a significant Type X Phase interaction (F(9,324)=4.20, p<.001), with a significant linear trend for Phase interacting with a quadratic trend for Type (F(1,36)=36.27, p<.001) and a significant linear trend for Phase interacting with a cubic trend for Type (F(1,36)=7.64, p<.01). These interactions were complex and indicated that while there is a general tendency for arousal to decrease across phases, the phase during which the change occurs depends on the type of stimulus: adult arousal decreases significantly from 0-1 then recovers in Phase 2 to Baseline level and maintains this level in Phase 3. Arousal to nonviolent and moderate violent categories decreases from 0-2 and maintains at the same level in Phase 3, and arousal to extreme violence does not change from 0-1, decreases from 0-2, but increases to the baseline level in Phase 3 (Table 1 presents the means for this analysis and Figure 3 illustrates the interaction; refer to Appendix section for all figures).

In summary, there were no significant differences between groups on the audio assessment. There were significant changes across phases depending on the type of stimuli. Responses to no violence and moderate violence stimuli decreased from 0-2 and showed no further decrease at Phase 3. Adult arousal decreased from 0-1 but returned to Baseline at Phase 2 and maintained its baseline level. In addition, there was a decrease in arousal to audio stimuli as violence increased.

Table 1
Mean Responses To Audio Assessment

	PHASE			
STIMULI	0	1	2	3
Adult	.55	.45	.48	.51
No Violence	.60	.49	.42	.41
Mod. Violence	.50	.45	.39	.38
Ext. Violence	.40	.37	.33	.36

3. Sexual Activities Card Sort - Revised. On this measure of sexual interest, each item was rated on a 7-point Likert-type scale, 1 (Very Attractive) to 7 (Very Unattractive). Mean scores were determined for each scale. Mixed model ANOVAs were conducted comparing scores on three deviant subscales (Pedophilia, Incest, & Paraphilia) to scores on the Adult Consenting Scale. The results of the analysis of the Pedophile subscale appear in Table 2 and are representative of other results. For all subscales, there was a significant main effect of Phase, a significant main effect of Type (deviant versus nondeviant) and a significant Type by Phase interaction. For the Pedophile subscale, the main effects for Phase (F(3,102)=10.41, p<.001), and Type (F(1,34)= 125.14, p<.001) were both significant. Also, for the same

scale, the Type X Phase interaction, (F(3, 102) = 14.40, p<.0 01) was significant. Subjects showed a significant increase in their rating of the deviant categories (less attractive) across phases, while their ratings of nondeviant categories did not change significantly. In all cases, most of the change occurred in the first phase of treatment. Different superscripts indicate statistically significant differences between means at the .05 level. The same superscript in different means indicates no significant differences.

Table 2
Mean Responses To Sexual Activities Card Sort

	PHASE 0 PRE	PHASE 1 RET	PHASE 2 RP/CF	PHASE 3 IFU
Child	4.75^{a}	5.58^{b}	5.92^{bc}	6.18^{c}
Adult	2.16^{d}	2.20^{d}	2.12^{d}	2.18^{d}

In summary, groups did not differ significantly on this measure. However, ratings of deviant categories were less attractive across phases 0-3, where ratings to nondeviant categories did not change significantly. As with the physiological measures, most change occurred from 0-1.

4. Symptom Checklist 90 (SCL-90). For the purpose of these analyses, four scales: Interpersonal Sensitivity, Depression, Anxiety, and Anger-Hostility were of interest as they were thought to be most sensitive to the expected changes resulting from treatment interventions in RET. The means for this analysis are in Table 3. There were no pretreatment differences among these variables.

The 0-3 analysis yielded a significant group difference was found on only one variable. Es scored significantly lower than Cs on Anxiety (F (1,32) = 7.96, p<.01). The means for Es and Cs were 1.82 and 1.45, respectively.

Phase effects were significant for Depression (F(3,99) = 6.11, p<.01), Anxiety (F(3,99) = 5.97, p<.01) and Anger/Hostility (F(3,99) = 2.98, p<.05). Subjects showed a reduction over time in their perceptions of their own pathology as measured by each of these three variables. Subjects tended to score low on all four measures of pathology across treatment phases. That is, scores ranged between "slight" to "mild" levels of pathology as indicated by behavioral anchors on the rating scale.

Table 3
SCL - 90
Table of Means

	Phase 0	Phase 1	Phase 2	Phase 3
Depression				
Control	2.23	2.18	1.93	1.99
Experimental	2.00	1.84	1.72	1.71
Anxiety				
Control	1.98	1.88	1.64	1.78
Experimental	1.62	1.43	1.43	1.34
Anger-Hostility				
Control	1.63	1.56	1.52	1.46
Experimental	1.60	1.33	1.39	1.34
Interpersonal Sensitivity				
Control	2.17	2.26	1.94	2.15
Experimental	1.97	1.80	1.78	1.72

In summary, Es rated themselves lower on anxiety than Cs. Both Es and Cs showed significant decreases in depression, anxiety, and anger/hostility across phases, although scores on these measures all tend to be low, and not indicative of clinical levels of pathology.

5. Self-Efficacy Scales. These scales measured the degree that clients believed they could successfully cope in high risk situations. Three variables were measured: frequency of encountering high risk situations (Opportunity); temptation to molest (Temptation) and perceived ability to resist temptation (Confidence). Each item is rated on a 7-point Likert scale, 1 (not in past year/not tempted/not at all) to 7 (at least once daily/extremely tempted/extremely confident). A total score was determined for each of the scales. Mean responses to the Self-efficacy scales appear in Table 4.

There were no differences between Es and Cs on these variables. Both groups tended to change across treatment phases, reporting fewer opportunities: (F(3,78)=5.29, p<.01), with a significant linear trend (F(1,26)=9.34, p<.01), and more temptations (0-2 analysis only): (F(2,88)=3.85, p<.05), with a significant linear trend (F(1,44)=5.02, p<.05). Scores on confidence did not change significantly across phases.

Table 4
Mean Responses To Self-Efficacy Scales

	PHASES			
	0	1	2	3
Opportunity	2.92	2.78	2.51	2.53
Temptation	4.82	5.02	5.28	5.07
Confidence	4.86	5.38	5.25	5.32

Item No. 12, page 8

2) Type (F(1,46) 7.82, p<.01), indicating that clients rated themselves higher than therapists. (Mean ratings = .62 and .49, respectively).

3) Block X Type (F(4,184)=4.49, p<.05) with a significant linear trend, (F(1,46)=4.49, p<.05), quadratic trend (F(1,46)=5.84, p<.05) and cubic trend (F(1,46)=7.87, p<.01), indicating that while clients' ratings of themselves were always significantly higher than therapists' ratings, with the exception of B4, therapists perceived clients as improving at a higher rate across blocks than clients perceived themselves.

The means representing the Type X Block effect are presented in Table 9 (LSD = .04).

Table 9
Therapist And Client GAS Ratings For Phase 2

	BLOCKS				
	B1	B2	B3	B4	B5
Client	.39	.55	.65	.72	.78
Therapist	.18	.43	.55	.60	.68

In summary, for Phase 1 GAS, Es rated themselves higher than Cs across blocks. There were no significant differences between Es and Cs on Phase 2 GAS. Both Es and Cs showed significant improvement across treatment blocks. Clients tended to give themselves higher ratings than therapists. Figures 4-7 illustrate the findings of the GAS scales for Phases 1 & 2, respectively.

3. Daily Self-Reports (DSRs). Clients recorded daily frequency of deviant and nondeviant (a) fantasies, (b) masturbations, and (c) sexual acts. A pretreatment baseline mean and means for the week ending the day before measurement sessions were calculated for each dimension and incorporated into the data analyses. Thus, a Baseline mean, five weekly means from Phases 1, five weekly means from Phase 2, and six weekly means from Phase 3 were obtained. Due to the low frequency of reporting deviant and nondeviant activities (e.g., the majority of clients reported $\leq$ 1 activity per week), these data were analyzed using nonparametric statistics. Means were averaged and ranked for analyses. A Mann Whitney U Test was conducted to compare Es and Cs at each phase. The results of this analysis revealed pretreatment differences in which Es reported more deviant fantasies than Cs (Mean Ranks = 41.96 and 29.04, respectively, Z= -3.00, p <.01). Also during Phase 1, Es reported more deviant masturbations than Cs (Mean ranks = 35.58 and 30.50, respectively, Z=-2.34, p <.05). No differences between groups were detected in Phases 2 or 3.

A Friedman 2-way Test compared the mean ranks from Baseline to Phase 3 for Es and Cs separately. The results of the analysis for Es yielded a significant decrease in deviant fantasies across phases (Chi-Square=10.22, p<.05), mean ranks = 3.32, 2.44, 2.24, and 2.00, respectively). No other variables were significant. The results of this analysis for Cs yielded no significant difference in mean ranks from 0-3.

A Wilcoxin Matched Pairs Test was performed to compare the mean ranks in each phase with those in each of the other phases. Groups were analyzed separately. Es showed significant decreases in deviant fantasies in the analyses of 0 with 1, 1 with 2, and 2 with 3. They showed significant decreases in deviant masturbations in 0 with 1, 0 with 2, and 0 with 3. Es also reported a significant increase in nondeviant fantasies in 0-1, and reduction in deviant masturbation in 0-1 and 1-2, and an increase in non-deviant acts from 1 to 3. Figures 8 and 9 present results of the Wilcoxin Signed-Ranks for Daily Self Reports illustrated as percent of clients reporting changes in frequency of reporting deviant fantasies and masturbations. A plus sign (+) indicates an increase in frequency and a minus sign (-) indicates a decrease in frequency.

Item No. 12, page 9

Overall, the results of these nonparametrics show that the most change occurred in the reporting of deviant fantasies and deviant masturbations, with Es reporting more improvement at various time periods than Cs.

Post-Treatment and Other Outcome Measures

1. Proficiency Tests. The RET and RP proficiency tests (20 questions each) consist of multiple-choice and fill-in-the-blank questions. These tests were administered at Termination and additionally served as a measure of treatment integrity; that is, to ensure that clients not assigned to RP were not inadvertently exposed to RP concepts by the therapists. A total score was determined for each test. Independent t-tests were performed to test the difference between Es and Cs on each proficiency test. There was no significant difference between mean scores for Es and Cs on the RET proficiency test (Means for Es and Cs = 16.82 and 16.15, respectively, $t(46) = .87$). That is, most clients achieved a score of 16 out of 20 on this measure. However, as expected, Es scored significantly higher than Cs on the RP proficiency test ($t\ (46) = -5.89$, $p < .001$, Means = 16.05 and 11.40, respectively), confirming that Cs were not inadvertently exposed to RP concepts.

2. Situational Competency Test. Subjects' responses to 14 high risk situations were scored across 10 dimensions including: the relevancy of the response, use of assertive behavior, use of avoidance or escape, the complexity of the response, and the effectiveness of the response. Scaled scores for each of the 10 dimensions, each of the 14 situations, and total scores were determined for each client. The total scores were analyzed using Independent t-tests. Es scored higher than Cs on this measure; however, the difference was not significant at the .05 level ($t\ (47) = -1.95$, $p = .057$, 2-tailed means for Es and Cs = 151.68 and 139.41 respectively). To test the differences between Es and Cs on the various subscales of the SCT, a Multivariate Analysis of Variance was performed on the 10 evaluative dimensions. The overall results of the MANOVA yielded a Multivariate $F(10,38)$ of 1.88, $p = .08$ univariate F-tests from this analysis of the ten evaluative dimensions revealed a significant difference for the variable, Complexity, with Es scoring higher than Cs ($F\ (1, 47) = 7.83$, $p < .01$, Means = 9.95 and 6.85, respectively). A Multivariate Analysis of Variance was also performed on the 10 situations. Although the results were not significant (Multivariate $F(10,33) = 1.2$, $p > .10$), Univariate F-tests for the 14 situations revealed that Es performed significantly better than Cs on 3 situations: a) #4, daily arguments with mother, ($F = (1,46) = 5.81$, $p < .05$, Means = 11.14 and 9.35, respectively), b) #8, a child showing evidence of sexual knowledge/interest, ($F(1,46) = 8.97$, $p < .01$, Means = 10.86, and 8.88) and c) #14, a direct invitation to have sex with a child, ($F(1,46) = 4.80$, $p < .05$, Means = 11.82 and 10.15, respectively). That is, Es performed better than Cs in those situations presenting the highest risk factors.

3. Client Satisfaction Scale. This scale consisted of 8 questions each rated on a 5-point Likert scale, 1 (not important/not at all) to 5 (extremely important/definitely). Each question was considered separately and analyzed with independent sample T-tests. The results of independent sample T-tests for Phase 1 revealed no significant differences between groups in satisfaction with treatment. Clients thought that services met their treatment needs (Mean = 4.31), treatment staff were considerate (Mean = 4.63), believed in the overall treatment program (Mean = 4.18), believed that treatment would help them stop offending (Mean = 4.65), believed that rational emotive therapy was important (Mean = 4.12), and that the lab assessment was moderately important (Mean = 3.40). In Phase 2 (RP/CF), Cs scored higher than Es in response to whether services met their treatment needs ($t(21) = 2.10$, $p < .05$), Means = 4.67 and 4.18, respectively). Cs also scored significantly higher than Es in their perception of the importance of RET (Means = 4.75 and 3.54, $t(21) = 2.21$, $p < .05$). Both groups thought that followup treatment was moderately important (Mean = 3.88).

4. Predictor Scale. This instrument was piloted to evaluate clients on various factors felt to be predictive of relapse and included both historical and current factors, e.g., history of alcohol abuse, total number of victims, percentage of current deviant masturbatory fantasies, etc. This scale was completed at Baseline and Termination only. The scale was comprised of six subscales: Deviant Attraction, Severity of

sexually deviant behavior, Violence Potential, Alcohol Use, Drug Use, and Stability. Internal consistency reliability (Cronbach's alpha) was calculated for the total score at baseline (alpha = .77) and termination (alpha = .85). The subscales of the Predictor Scale were used in a correlational analysis to determine the degree of association with a measure of recidivism. The results are presented in the section discussing the Client Follow-up Questionnaire.

5. Significant Other Rating Scale (SORS). This instrument was piloted in this study. The measure consists of 25 questions rated on an eight-point Likert scale according to the frequency of occurrence of behaviors associated with offending (1 = never and 8 = once/day). The SORS has 5 subscales: Activities with Children, Activities with Adults, Asocial Activities, Personal Adjustment, and Irresponsible Behavior. The SORS was initially mailed to significant others at Baseline and subsequent reassessment phases. However, the response rate diminished across phases allowing analysis of Baseline and Phase 1 data only. The analysis of this data was problematic because significant others changed across phases. Internal consistency reliability was obtained on the entire test as well as each of the subscales for Phases 0 and 1 using Chronbach's alpha. The standardized item alpha for Baseline was .82 and for Phase 1 was .70. However, alphas for some subscales from Phase 0 to Phase 1 were unstable, perhaps reflecting the diversity of the input from different raters. The subscales from the SORS were also used in a correlational analysis with measures of recidivism in the Client Follow-up Questionnaire.

6. The Client Followup Questionnaire. This questionnaire was designed to collect preliminary recidivism data on CPCM clients. Questions were designed to elicit information on the number of investigations/arrests/convictions for sex and non sex crimes and a rating of community adjustment for each client. 53 Questionnaires were mailed to probation officers of record (for those clients on probation) who were asked to rate the client's activity within the last 6 months (or since treatment termination). Forty-five questionnaires were returned. Frequency of recidivism activity was determined for each of the major categories. Each activity represents a different method of conceptualizing recidivism. Table 10 shows that the seven sex crimes investigated resulted in three arrests and two convictions. The same client was investigated, arrested and convicted of non-sex crimes. The following results were obtained as shown in Table 10.

Table 10
Recidivism Rates Since Treatment Termination

Sex Crime Investigations:	7/45	15.5%
Sex Crime Arrests:	3/45	6.6%
Sex Crime Convictions:	2/45	4.4%
Non Sex Crime Investigations:	1/45	2.2%
Non Sex Crime Arrests:	1/45	2.2%
Non Sex Crime Convictions:	1/45	2.2%
Violations of Probation:	8/45	17.8%

In addition, a total score was obtained by summing the number of activities for each category reported for each client. This total score was correlated with scores on RET and RP Profiency Tests, TGAS and CGAS measures, Scores on the SCT, Deviant Arousal Change Scores, subscales from the Predictor Scale and subscales from the Significant Other Rating Scale. The Pearson correlations coefficient analyses produced three significant findings:

a. There was a significant moderate negative correlation between recidivism and scores on the RP proficiency test ($r = -.39$, $p<.05$, $n = 33$). Higher scores on RP were related to lower scores on the recidivism measure.

b. There was a significant moderate positive correlation between recidivism and the Alcohol Use subscale from the analysis of the predictor scale administered at treatment termination ($r = .33$, $p<.05$, $n = 39$).

Item No. 12, page 11

c. There were moderate to high positive correlations between recidivism and three of the five SORS subscales: Activities with Children (baseline score, $r = .51$, $p<.01$, $n = 34$); Irresponsible Behavior (baseline score, $r = .39$, $p<.05$, $n = 34$); and Asocial Activities (Phase 1 score, $r = .60$, $p<.01$, $n = 22$).

The correlations of recidivism with GAS scales, RET proficiency, SCT, change in deviant arousal, and most of the subscales from the Predictor Scale were not significant.

Considering the above correlations, a step-wise multiple regression analysis was performed forcing the eight variables most correlated with recidivism into the regression equation, and using a step-wise deletion procedure. The final equation included RP proficiency, Activities with Children (SORS, phase 0) and Asocial Activities (SORS, phase 1) into the regression equation at steps 1,2, and 3, respectively. This equation accounted for 51% of the variance in recidivism (standard betas = -.27, .55, .37 for variables 1, 2, and 3 respectively; $R^2 = 51$, ($F(3,39)=13.55$, $p<.01$).

Although this analysis is exploratory it points to two important areas of further inquiry in the prediction of recidivism:

a. The learning of relapse prevention concepts and practices may be more important than the reduction of deviant arousal in predicting recidivism.

b. Reports from significant others regarding actual client behaviors (e.g., the frequency of activities with nonrelative children, time that is not accounted for, the use of alcohol) may be useful predictors of recidivism.

Summary and Discussion of Results

Although subjects were randomly assigned to groups, significantly more homosexual pedophiles were assigned to E than C. Consequently, at baseline, Es had higher arousal to male slides than Cs (which was corrected with relative arousal scores) and reported more deviant sexual fantasies. Also at baseline, Es were rated by therapists as displaying more interpersonal sensitivity (focus on feelings of personal inadequacy and inferiority). In short, Es seemed to present more serious pathology than Cs prior to treatment. In spite of this pre-treatment disadvantage, among the group differences that were detected, Es performed better than Cs.[4]

Classification. With respect to the classification of pedophiles into subgroups, results indicate that the Card Sort measure performs about as well as the physiological measures in separating heterosexual from homosexual pedophiles who respond to physiological assessment (responders). The Card Sort is also useful as a gauge of treatment progress. That is, subjects report a decrease in attraction to stimuli that parallels their decrease in deviant sexual arousal. One could therefore effectively argue for the use of the card sort technique in lieu of physiological measures in cases where such measures are objectionable. The Card Sort might also be useful as an adjunctive tool with nonresponders. However, too few cases of nonresponders were available for analysis to confirm or reject this hypothesis.

Between Phase Measures of Outcome. Very few between group differences were detected using the between phase measures. Groups responded similarly to self-report and psychophysiological assessment measures (with the exception of selected subscales of the Brief Hopkins and SCL-90). Overall, all subjects

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[4] One might attribute the change in Es relative to Cs to the fact that therapists were not blind to experimental hypotheses and created a higher expectation for treatment success in Es. The results of the Client Satisfaction Survey presents a counter to this argument as Cs scored higher than Es in their perception of the program meeting their treatment needs (Phase 2) and in their perception of the importance of RET (Phase 2). However, the possibility of these factors operating can not be ruled out.

Item No. 12, page 12

showed improvement across phases with the most improvement being detected from baseline to phase 1. For the Slide Assessment and the Sexual Activities Card Sort, subjects showed a decrease in responses to deviant categories (sex with children), while responses to nondeviant categories (consenting adult) were essentially unchanged. The audio assessment detected a decrease in adult arousal from Baseline to Phase 1 which returned to Baseline levels in subsequent phases. Inspection of the data suggests that this effect of aversive conditioning on adult arousal may be more pronounced in the OA than the VS group. Another important finding from the audio assessment is that sexual arousal decreases as the depiction of violence in the stimuli increases. This supports the finding that child molesters are by and large not attracted to violent sexual acts with children.

Within Phase Measures of Progress. The within phase measures of treatment progress were better for detecting differences between groups. On the RET GAS scales, Es rated themselves higher than Cs across treatment blocks, indicating a greater mastery of materials.

The analysis of the measurement data detected a greater reduction in arousal (deviant and nondeviant) from baseline to week 20 in Es compared to Cs, lending some support to the effectiveness of behavior therapy during Phase 1. Overall, considering the total amount of change across phases, Es showed more reduction in deviant arousal compared to Cs, whereas nondeviant arousal changed very little; Cs showed about the same amount of negligible change in deviant and nondeviant arousal across phases. This finding further lends support to the relative efficacy of the package, RET/BT+RP in the reduction of deviant arousal compared to RET+CF.

The nonparametric analysis of the Daily Self-Reports also parallel the above findings. Es showed a significant decrease in deviant behaviors (fantasies and masturbations) at more time periods than Cs. Reports of deviant and nondeviant activities were sporadic. Clients were reluctant to report sexual acts, although less reluctant to report fantasies. For these reasons, the DSR instrument may have been just as useful if modified to track the reporting of deviant fantasies and masturbations only, and on a less frequent basis (perhaps 1 week in each month).

The self-report measures (both between and within phases) in this study all seemed to be influenced by a social desirability response set. For example, on the self-efficacy ratings, clients reported fewer opportunities to engage in deviant behavior over time. They acknowledged a moderate amount of temptation in these situations, but felt very confident that they could handle the situations presented. When asked how well they knew material (e.g., GAS scales), clients indicated a higher level of mastery than therapists believed them to have achieved. Both therapists and clients rated clients as improving over time (i.e., Outcome of Therapy, GAS scales, Global Improvement Ratings). DSR ratings revealed unrealistically infrequent fantasy and masturbation activity. Perhaps the progress reflected in these ratings are more a reflection of the clients knowledge that he must successfully complete a program, and the therapists' desires to reflect the good service they believe themselves to have rendered to the clients than an accurate measure of therapeutic change.

Post-treatment and Other Measures. Perhaps the most promising results were found in the analysis of the inventories that were added later in the project as more sensitive measures of treatment outcome. The results of these measures revealed that the treatment interventions were received as intended. That is, Es=Cs in their knowledge of RET and Es>Cs on their knowledge of RP. There was some evidence to suggest that Es scored higher than Cs on the situations that presented the most risk on the SCT, (e.g., direct invitations to have sex with a child.)

Additionally, although recidivism data have not yet been analyzed for between group differences, subjects who score higher on RP proficiency had lower recidivism scores. The results of this study also indicate that the Predictor Scale and measures of deviant change do not seem to work as well as the SORS in predicting recidivism. In fact it appears that early reports from significant others regarding client activities (e.g., socializing with nonrelative children, engaging in asocial behaviors) may be more predictive of relapse than clinical variables. However, further work is needed in improving the psychometric properties of the SORS before conclusions are drawn.

Item No. 13

Serendipitous Findings:

1.) Compliance with Behavior Therapy

To assess the degree of compliance with behavior therapy, progress notes of clients who had completed BT were examined and rated according to 5 behavioral descriptions of compliance (see Appendix C-20). Mean scores were obtained for lab sessions and homework sessions. These means were correlated with Baseline to Phase 1 change scores obtained from psychophysiological measures. The findings were:

1. There were no significant differences in the level of compliance for OA vs. VS.

2. Using percentage scores, level of compliance was not significantly correlated with change scores in deviant or nondeviant arousal as measured by slide and audiotape assessments, and measurement sessions.

3. In analyses of measurement data of responders (those clients who achieved at least 20% FE to any stimuli), compliance with homework was significantly correlated with changes in nondeviant arousal ($r = .68$, $p < .01$, 1 - tailed), indicating that higher compliance was related to increased adult arousal.

4. In analysis of slide and audio assessments with responder, change in relative arousal to female deviant slides was correlated with compliance with homework sessions ($r = .50$, $p < .01$, 1 - tailed), compliance with homework sessions was also correlated with change in relative arousal to nonviolent female stimuli ($r = .46$, $p < .05$, 1 - tailed.)

These findings provide some evidence of the importance of compliance with behavior therapy in obtaining desired treatment outcome. Further research is needed with this measure to confirm these findings.

2.) Effects of OA and VS on Nondeviant Arousal

A post-hoc ANOVA was conducted on relative arousal scores to adult stimuli from the audio assessment for OA and VS only. There was a significant Group X Phase effect ($F(3,51) = 3.13$, $p < .05$), with a significant linear trend for phase interacting with Group ($F(1,17) = 9.88$, $p < .01$). This effect indicated that VS had a greater increase in adult arousal than OA across treatment phases.

This is an important finding because VS is a less intrusive procedure than OA, appears to be equally effective in reducing deviant arousal (see Results Section), and has the added benefit of increasing adult arousal. Further research is needed with a larger sample size to confirm these findings.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

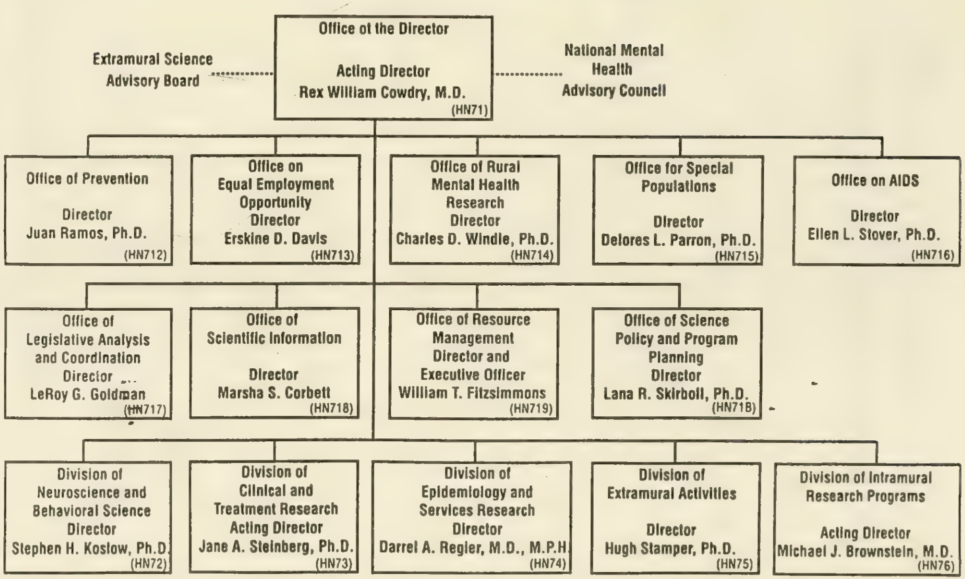
NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

FY 1996 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	5
Budget mechanism table	6
Summary of changes	8
Budget authority by object	10
Administrative costs	12
Significant items in House Appropriations Committee Reports	13
Authorizing legislation	14
Appropriation history	15
Budget authority by activity	16
Justification:	
A. General statement	17
B. Extramural research	19
C. Intramural research	29
D. Research management and support	31
E. Detail of full-time equivalent employment (FTE)	33
F. Detail of end-of-year employment	34

2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Institute of Mental Health


Extramural Science Advisory Board
Office of the Director
Acting Director
Rex William Cowdry, M.D.
(HN71)
National Mental Health Advisory Council
Office of Prevention
Director
Juan Ramos, Ph.D.
(HN712)
Office on Equal Employment Opportunity
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Erskine D. Davis
(HN713)
Office of Rural Mental Health Research
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Office on AIDS
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Hugh Stamper, Ph.D.
(HN75)
Division of Intramural Research Programs
Acting Director
Michael J. Brownstein, M.D.
(HN76)

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

For carrying out section 301 and title IV of the Public Health Service Act with respect to mental health, [$543,550,000] *$558,580,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$613,444,000	$543,550,000	$558,580,000
Section 205 Procurement reduction......................	---	-358,000	---
Section 207 Rent reduction........	---	-4,000	---
Section 513 S&E reduction.........	---	-199,000	---
Subtotal, Adjusted Appropriation................	613,444,000	542,989,000	558,580,000
Comparative transfer to the Office of AIDS Research, NIH for HIV Activities.......	-87,182,000	---	---
Comparative transfer to the Office of the Director, NIH for Accounting Services..	-286,000	-286,000	---
Comparative transfer to other NIH Institutes for Management Fund adjustment.............	-219,000	-863,000	---
Subtotal, adjusted budget authority..................	525,757,000	541,840,000	558,580,000
Unobligated balance, lapsing......	-92,000	---	---
Total obligations.............	525,665,000	541,840,000	558,580,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1994--$8,337,000; 1995--$12,000,000 and 1996--$12,000,000.

Also excludes funding for HIV activities: FY 1995--$89,435,000; FY 1996--$93,556,000, included in the Office of AIDS Research, NIH.

Note: Excludes $109,000 in FY 1994 and $80,000 in FY 1995 for royalties

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Mechanism

Research grants:	1994 Actual No.	1994 Actual Amount	1995 Appropriation No.	1995 Appropriation Amount	1996 Estimate No.	1996 Estimate Amount
Research projects:						
Noncompeting	839	$190,303,000	856	$202,574,000	924	$213,893,000
Administrative supplemental	(32)	2,379,000	(32)	2,474,000	(32)	2,573,000
Competing projects:						
Renewal	103	24,400,000	95	23,920,000	89	22,968,000
New	259	47,718,000	240	46,779,000	226	44,918,000
Supplemental	7	742,000	6	727,000	6	698,000
Subtotal, competing	369	72,860,000	341	71,426,000	321	68,584,000
SBIR/STTR	39	6,295,000	47	7,706,000	47	8,030,000
Subtotal, research projects	1,247	271,837,000	1,244	284,180,000	1,292	293,080,000
Research centers:						
Spec./comp. centers	53	51,376,000	53	53,488,000	53	55,734,000
Other Research:						
Research career programs	263	27,226,000	263	27,988,000	263	28,800,000
Cooperative clinical research	16	4,288,000	16	4,408,000	16	4,536,000
Other research related	64	19,773,000	62	20,002,000	62	20,583,000
Subtotal, other research	343	51,287,000	341	52,398,000	341	53,919,000
Total, research grants	1,643	374,500,000	1,638	390,066,000	1,686	402,733,000

Training:						
Individual awards:						
Noncompeting	135	2,455,000	119	2,085,000	119	2,146,000
Competing	111	1,932,000	127	2,425,000	127	2,495,000
Subtotal, individual	246	4,387,000	246	4,510,000	246	4,641,000
Institutional awards:						
Noncompeting	683	16,346,000	714	18,236,000	714	18,765,000
Competing	200	5,499,000	169	4,221,000	169	4,343,000
Subtotal, institutional	883	21,845,000	883	22,457,000	883	23,108,000
Total, training	1,129	26,232,000	1,129	26,967,000	1,129	27,749,000
Research & development contracts	40	9,884,000	40	10,160,000	40	10,455,000
SBIR/STTR	(6)	(652,000)	(2)	(764,000)	(2)	(854,000)
	FTEs		FTEs		FTEs	
Intramural research program	574	84,466,000	599	84,016,000	591	86,419,000
Research management and support	326	30,675,000	298	30,631,000	297	31,224,000
Extramural construction	---	---	---	---	---	---
Total, NIMH	900	525,757,000	897	541,840,000	888	558,580,000
(Clinical Trials)		(48,689,000)		(50,152,000)		(51,722,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Summary of Changes

1995 Estimated budget authority	541,840,000
1996 Estimated budget authority	558,580,000
Net Change	+16,740,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural:				
a. Within grade increase		$35,495,000		+$447,000
b. One more day of pay		35,495,000		+133,000
c. Annualization of January 1995 locality pay raise		35,495,000		+222,000
d. January 1996 pay increases		35,495,000		+807,000
e. FECF, Unemployment compensation		35,495,000		+5,000
f. Service and supply fund increase		8,611,000		+263,000
g. Payment for centrally funded services		28,519,000		+970,000
h. Increased cost of laboratory materials and supplies		10,899,000		+326,000
i. DHHS Working Capital Fund decrease		327,000		-10,000
j. FTS decrease		165,000		-32,000
Subtotal				+3,131,000
2. Research Management & Support:				
a. Within grade increase		19,687,000		+303,000
b. One more day of pay		19,687,000		+76,000
c. Annualization of January 1995 locality pay raise		19,687,000		+86,000
d. January 1996 pay increases		19,687,000		+349,000
e. FECF, Unemployment compensation		19,687,000		+3,000
f. Service and supply fund increase		3,702,000		+125,000

Summary of Changes--continued

	1995 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
g. Payment for centrally funded services		1,358,000		+40,000
h. Increased cost of material and other supplies		5,527,000		+155,000
i. DHHS Working Capital Fund decrease		252,000		-3,000
j. FTS decrease		105,000		-19,000
Subtotal				+1,115,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting	856	205,048,000	+68	+11,418,000
b. Competing	341	71,426,000	-20	-2,842,000
c. SBIR/STTR	47	7,706,000	---	+324,000
Total, research projects	1,244	284,180,000	+48	+8,900,000
2. Research centers	53	53,488,000	---	+2,246,000
3. Other research	341	52,398,000	---	+1,521,000
4. Research training	1,129	26,967,000	---	+782,000
5. Research and development contracts	40	10,160,000	---	+295,000
	FTE		FTE	
6. Intramural research program	599	84,016,000	-8	-728,000
7. Research management & support	298	30,631,000	-1	-522,000
Subtotal				+12,494,000
Total changes				+16,740,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority By Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	897	888	-9
Full-time equivalent of overtime and holiday hours.......	5	5	--
Average ES salary..................	$109,594	$112,241	+$2,647
Average GM/GS grade................	10.2	10.2	---
Average GM/GS salary...............	$44,874	$45,958	+$1,084
Average salary, grades established by PHS Act of 1955 (42 USC 207)..	$53,173	$54,457	+$1,284
Average salary of ungraded positions........................	$34,785	$35,625	+$840
Personnel compensation:			
Full-time permanent................	$30,169,000	$30,721,000	+$552,000
Other than full-time permanent.....	8,774,000	9,042,000	+268,000
Other personnel compensation.......	1,686,000	1,737,000	+51,000
Special personnel service payments.	4,736,000	4,881,000	+145,000
Total personnel compensation....	45,365,000	46,381,000	+1,016,000
Personnel benefits....................	9,642,000	9,855,000	+213,000
Benefits for former personnel.........	175,000	180,000	+5,000
Travel and transportation of persons..	836,000	846,000	+10,000
Transportation of things..............	161,000	163,000	+2,000
Rental payments to others.............	1,304,000	1,320,000	+16,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Communications, utilities, and miscellaneous charges...............	$1,665,000	$1,646,000	-$19,000
Printing and reproduction.............	1,061,000	1,074,000	+13,000
Other services:			
Consulting services.................	118,000	119,000	+1,000
Other services......................	7,157,000	7,432,000	+275,000
Purchases from government accounts..	38,913,000	40,274,000	+1,361,000
Research & development contracts....	10,160,000	10,455,000	+295,000
Supplies and materials................	5,871,000	5,944,000	+73,000
Equipment.............................	2,167,000	2,195,000	+28,000
Grants, subsidies, & contributions....	417,033,000	430,482,000	+13,449,000
Land and Structures...................	15,000	15,000	---
Insurance claims and indemnities......	194,000	196,000	+2,000
Interest and dividends................	3,000	3,000	---
Total, budget authority by object	541,840,000	558,580,000	+16,740,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Administrative Costs

(Dollars in Thousands)

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Personnel Compensation:			
Full-time Permanent (11.1)..............	$30,169,000	$30,721,000	+$552,000
Other than Full-time Permanent (11.3)....	8,774,000	9,042,000	+268,000
Other Personnel Compensation (11.5)......	1,686,000	1,737,000	+51,000
Special Personnel Service Payments (11.8)	4,736,000	4,881,000	+145,000
Total Personnel Compensation (11.9)....	45,365,000	46,381,000	+1,016,000
Civilian Personnel Benefits (12.1).........	9,642,000	9,855,000	+213,000
Benefits to Former Personnel (13.0)........	175,000	180,000	+5,000
Travel (21.0)............................	836,000	846,000	+10,000
Transportation of Things (22.0)...........	161,000	163,000	+2,000
Rental Payments to Others (23.2)..........	1,304,000	1,320,000	+16,000
Communications, Utilities, and Miscellaneous Charges (23.3)............	1,665,000	1,646,000	-19,000
Printing and Reproduction (24.0)..........	1,061,000	1,074,000	+13,000
Consulting Services (25.1)................	118,000	119,000	+1,000
Other Services (25.2).....................	7,157,000	7,432,000	+275,000
Purchases from Government Accounts (25.3)..	38,913,000	40,147,000	+1,234,000
Research & Development Contracts (25.5)....	---	---	---
Supplies and Materials (26.0).............	5,855,000	5,928,000	+73,000
Total................................	112,252,000	115,091,000	+2,839,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Significant Item in the House Appropriations Committee Report

Item	Action Taken or to be Taken
1995 House Report	
Eating Disorders	
1. The House in its report 103-553, page 62 stated, "The Committee continues to be concerned about the prevalence of eating disorders, which disproportionately affect women. The Committee urges NIMH to continue to expand its research on eating disorders and to improve its efforts to communicate prevention and treatment strategies to health care providers and the lay public."	1. In addition to supporting research on the effectiveness of psychosocial and pharmacological treatments of eating disorders, NIMH, as part of its effort to disseminate sound, research-based information to the field, is convening a Scientific Advisory Group with three broad goals: first, to organize existing research and establish a scientific consensus; second, to develop the content appropriate for a professional education campaign; and third, to establish messages appropriate for public education. NIMH also is actively collaborating with the DHHS/McKnight Foundation eating disorders education effort.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Authorizing Legislation

	PHS Act/ Other Citation	U.S.Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation...	Section 301	42§241	Indefinite	$514,873,000	Indefinite	$530,831,000
National Institute of Mental Health...	Title IV, Part C	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards..........	Section 487(D)	42§288	Such sums as necessary	26,967,000	Such sums as necessary	27,749,000
Total, Budget Authority.......				$541,840,000		$558,580,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	n/a	n/a	$574,803,000	$583,651,000 2/
1994	$576,015,000	$613,444,000	613,444,000	613,444,000
1995 3/	545,223,000	541,687,000	543,687,000	542,989,000 4/
1996 3/	558,580,000			

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIMH was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $4,723,000, $81,000, and $1,981,000.

3/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

4/ Excludes enacted administrative reductions of $358,000, $4,000, and $199,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Extramural research and training...............	---	$369,484	---	$385,530	---	$410,616	---	$427,193	---	$440,937		+$13,744
Intramural research.........	680	84,543	590	86,993	574	84,466	599	84,016	591	86,419	-8	+2,403
Research management and support.................	349	30,118	358	31,895	326	30,583	298	30,631	297	31,224	-1	+593
Subtotal, obligations....	1,029	484,145	948	504,418	900	525,665	897	541,840	888	558,580	-9	+16,740
Unobligated balance, lapsing..............	---	199	---	291	---	92	---	---	---	---		
Total, budget authority..	1,029	484,344	948	504,709	900	525,757	897	541,840	888	558,580	-9	+16,740

Justification

National Institute of Mental Health

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
900	$525,757,000	897	$541,840,000	888	$558,580,000	-9	+$16,740,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute of Mental Health. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The research programs of the National Institute of Mental Health (NIMH) lead the Federal effort to identify the causes of--and the most effective treatments for--mental illnesses, which afflict more than one in five Americans. Mental illnesses cost the Nation over $148 billion each year in direct and indirect costs. For example, a recent study estimated that reduced productivity from depression amounted to $3,000 annually for each depressed worker or $180 for every U.S. employee. Severe mental illnesses, such as schizophrenia, affect approximately five million adult Americans annually, yet account for $14 billion, or 25 percent, of all annual Federal disability payments (Social Security Insurance and Social Security Disability Insurance). One result of NIMH research has been a new awareness that undiagnosed and untreated mental illness, in all its forms and with all of its consequences, is as damaging as physical illness is to the Nation's well-being.

NIMH research brings a unique multidisciplinary approach to the human brain and behavior in health and in illness, integrating findings from the neurosciences, basic behavioral sciences, clinical research, epidemiology, prevention research, and mental health services research. Within this overall approach, the Institute supports both basic research and research addressing the causes of and treatments for specific mental illness, such as schizophrenia, mood disorders, anxiety disorders, eating disorders, Alzheimer's disease, and childhood mental illnesses. NIMH research includes the mental health needs of special populations, including rural areas, racial and ethnic minority populations, and women. The Institute also provides data on the organization and financing of mental health services. The President's appropriation request of $558,580,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Mental Health during the last five years has been as follows:

	Amount	FTE
1991	$439,247,000	998
1992	484,344,000	1029
1993	504,709,000	948
1994	525,757,000	900
1995	541,840,000	897

Purpose and Method of Operation

The purpose of NIMH research is to generate new information about the causes, diagnosis, treatment, and prevention of mental disorders. This is accomplished through federal funding of direct intramural research and support for various extramural mechanisms. In addition, NIMH supports research training and career development, and research dissemination.

Overall Budget Policy

The FY 1996 budget request for NIMH is $558,580,000, an increase of $16,740,000, which is 3.1 percent over the comparable FY 1995 level of $541,840,000.

Within the request, funding for research project grants increases by 3.1 percent to $293,080,000 for 1,292 research project grants in the FY 1996 President's Budget Request as compared to $284,180,000 for 1,244 research project grants in the FY 1995 Appropriation. Continuing grants increase by 5.6 percent, while new and competing grants are decreased in funding by $2,842,000, or 4.0 percent, below the FY 1995 Appropriation. The number of competing research grants decreases from 341 to 321.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Average grant awards received a 4.0 percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The NIMH total request for research centers is $55,734,000 for 53 centers, a $2,246,000 increase. The budget permits funding the remaining extramural mechanisms with a 2.9 percent increase. The research training mechanism will fund the same number of FTTPs as in FY 1995, with a 2.9 percent increase in funds. Programmatic outputs for other research, research training, and contracts will remain approximately level in the total FY 1996 budget.

Funding for the NIMH intramural program is $86,419,000, an increase of $2,403,000 over the FY 1995 Appropriation of $84,016,000. FTES are 591 as compared to 599 in FY 1995.

The research management and support request is $31,224,000, an increase of $593,000 over the FY 1995 Appropriation of $30,631,000. FTES are 297 compared to 298 in FY 1995.

National Institute of Mental Health

Extramural Research

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$410,616,000	$427,193,000	$440,937,000	+$13,744,000

To coordinate and conduct its national program of extramural research and research training, NIMH program areas include: the fundamental knowledge base of neuroscience and behavioral science; clinical and treatment research; epidemiology and services research; and prevention research.

Funding for extramural programs during the last five years has been as follows:

	Amount
1991	$335,252,000
1992	369,509,000
1993	385,709,000
1994	410,616,000
1995	427,193,000

Rationale for the Budget Request

The FY 1996 extramural request will provide support for the following activities: research and research training, $440,937,000, an increase of $13,744,000 or 3.2% over the FY 1995 estimate of $427,193,000. The following are examples of current program activities and future plans.

The Brain and Behavior

Understanding brain function requires the integration of information from the level of the gene to the level of behavior. At every level there has been a flood of new information. For example, the discovery that nitric oxide (NO), a highly diffusible and reactive gas, is serving as a messenger molecule in the brain is leading to a deeper understanding of the complexities of brain function. A major reason for excitement has been the realization that because of its unique gaseous state, NO may allow a previously unknown form of communication between two neurons at the synapse--communication that could be important in memory. A recent advance in understanding this rapidly developing area has been the finding that transgenic mice that were given drugs blocking all NO synthesis developed memory deficits. These transgenic mice lacked the gene for a form of enzyme that synthesizes NO, but had normal memory and learning abilities. Therefore, the neurons in critical brain memory circuits must have developed redundant mechanisms to assure continued functioning--that is, they have more than one enzyme with which to make NO, a finding consistent with the theory that this gaseous molecule is vitally important to memory.

NIMH researchers have identified what may be the method our brains use to create particularly acute memories of emotional events. For example, remembering exactly where we were when President Kennedy was assassinated. This is the same alerting system used to make the body react to life-threatening emergencies, the so-called "fight or flight" response. These primitive survival reactions are caused by the release of the hormones adrenaline and noradrenaline, which also instruct the brain to take special note of the circumstance that set off the reaction. This research on the neurochemistry of memory in humans confirmed fifteen years of research with rats. These findings may have implications for education since they suggest that excitement is important for the storage of information. Furthermore, this mechanism helps to explain the intrusive memories that trouble people suffering from post-traumatic stress disorder, and may lead to ways of preventing or treating such disabling reactions to trauma.

Building on the vast explosion of findings from the area of brain and behavior research, NIMH will focus its research efforts on the following:

- Expanding our understanding of the multiple forms of the neurotransmitter receptors and the differential roles they may play in the etiology of and pharmacotherapy for schizophrenia. Such studies offer the opportunity to develop more effective and more specific antipsychotic medications.

- Increasing research on *in vivo* neuroimaging of brain functional neuroanatomy and neurotransmitter systems. These studies should ultimately reveal brain mechanisms and brain dynamics involved in the etiology and treatment of mental illnesses.

- Maximizing the new opportunities afforded by the accelerated mapping of the human genome to aid in identifying and sequencing the gene or genes responsible for the vulnerability to manic-depressive illness, schizophrenia, and Alzheimer's disease and expedite research on the interaction of inherited vulnerability and psychosocial antecedents of mood disorders.

It is easy, in this Decade of the Brain, to forget that psychological interventions have demonstrable, substantial, and long-lasting effects on neurobiological processes and even genetic expression. Some critics have impugned the clinical effectiveness of psychological treatment compared to drug treatment. However, psychological interventions from a variety of theoretical perspectives have demonstrated effectiveness, either alone or in combination with medications, for a wide variety of disorders. Years of research have shown the effects of psychological variables and procedures on neurotransmitter activity, cell receptor physiology, and other aspects of brain structure and function. NIMH research is continuing to search for the most effective combinations of biological and psychological treatments for specific mental disorders.

Depression, Mood Disorders, and Anxiety

Groundbreaking research by an NIMH grantee suggests that panic attacks may be caused by a defect in the body's natural suffocation alarm. About three million Americans suffer from spontaneous panic attacks--attacks that cannot be connected to a particularly fearful event or object. The classic symptoms of a panic attack include: shortness of breath, accelerated heartbeat, trembling, choking, and fear of dying, beginning suddenly and increasing in intensity within minutes. The suffocation alarm, considered to be located in the carotid body in the neck, monitors the amount of oxygen and carbon dioxide in the blood. The findings show that people who suffer panic attacks appear to have overly sensitive alarms that react to even small changes in the amount of carbon dioxide and oxygen in the body. This research suggests that when the false alarm is signaled the brain suppresses the respiratory system causing the classic panic attack symptoms. More research on this theory may point to novel uses of psychopharmacologic medications to attenuate this alarm system. Such treatments could offer hope for many people who suffer from this debilitating disorder.

Recently tabulated results from the largest population survey of mental disorders in U.S. history showed that more than 1 in 4 Americans have multiple symptoms of depression sometime in their lives. In one area of depression research, NIMH-funded scientists used PET to measure differences in regional cerebral blood flow in patients with unipolar depression compared to both those who had recovered from depression and healthy volunteers. Their findings suggest this may be a useful tool for diagnosing unipolar depression and determining who may be at risk for developing depressive symptoms. NIMH plans to focus research on the ways in which symptoms of depression are expressed in the primary care setting and on the barriers to proper recognition and treatment of depression in those settings. The Institute also plans to pursue leads based on the discovery that antidepressant drugs interact with the family of regulatory proteins known as G proteins, which could lead to entirely new targets for both biochemical and genetic studies and for development of new drug therapies.

Schizophrenia

Schizophrenia, the most devastating mental illness, affects 2 million people annually. NIMH research led to the discovery of the treatment clozapine, which has been shown to produce substantial savings in hospitalization costs, as well as to reduce the symptoms of the disease, improve the quality of life for patients, and reduce the probability of suicide by patients who had not been helped by other drugs. In a group of severely ill patients with treatment-resistant schizophrenia who were maintained on clozapine for over 2 years, total cost savings--treatment, housing, family burden, etc.--averaged $22,937 per year per patient. These savings were due almost entirely to a reduced need for hospitalizations.

Through increasingly precise methodologies and instrumentation, we are gaining knowledge of neurodevelopmental changes in the brain that lead to the appearance of schizophrenia in young adulthood. Recent findings in schizophrenia research have contributed to a leap forward in directions for exploration. These findings include:

- The measurement of the mesiotemporal brain structures, which include the hippocampus and amygdala, in chronic multiepisode, treatment-resistant schizophrenic men. The results showed reduced volumes in chronic patients that differed from that previously found in first-episode patients. In the chronic patients, there was an inverse correlation between volume and psychopathology, suggesting that positive psychotic symptoms, particularly thought disorganization and delusional thinking are associated with injury to this part of the brain.

- NIMH-funded investigators found that the combined density of dopamine D2 and D3 receptors is elevated by 10 percent in the brains of persons with schizophrenia, but that the density of dopamine D4 receptors is elevated six-fold. This study used brain tissue obtained from the NIMH-funded brain bank.

Child and Adolescent Mental Disorders

Previous research on service use by children and adolescents with mental health problems has shown that multiple service sectors are often involved: general health, education, child welfare, juvenile justice, substance abuse, and mental health. Community surveys have shown that between 6 and 16 percent of children and adolescents with diagnosable mental disorders received some type of mental health service in the past year. Much is still unknown about both the children who receive care and those who do not. NIMH has launched a Multi-Site Study of Mental Health Service Use, Need, Outcomes, and Costs in Child and Adolescent Populations (UNO-CAP). UNO-CAP aims to learn more about the types of services, efficacy, and cost effectiveness of mental health treatment for children and adolescents ages 4 to 17. In addition, this initiative will be used to gather national data on the prevalence and incidence of specific mental disorders among this population. This effort began in FY 1995 and involves four sites in the community study and a national survey. The project is proposed for 5 years with some projects that have incorporated longitudinal designs receiving funding beyond that period.

Mental Illnesses in Older People

At least 4 million Americans are estimated to suffer from Alzheimer's disease. The symptoms, such as memory loss and personality change, cause mental and emotional stress, and Alzheimer's patients often require the constant care of a family member. It is well documented that caring for a terminally or chronically ill relative, such as one with dementia, has serious effects on the well-being of the caregiver. Not surprisingly, caring for a person with this illness can cause significant, long-lasting stress. People who care for Alzheimer's patients report having more colds, flu and other respiratory illnesses. Emotional disturbances such as anxiety or major depression are common, affecting as many as 30 percent of the caregivers.

A recent study by NIMH-sponsored researchers found that the emotional and physical stresses that accompany caregiving can last up to two years beyond the death of the loved one with the illness. Family members who previously cared for a loved one with Alzheimer's disease reported identical levels of depression and stress to those currently caring for a loved one. This clinical depression is not confused with normal grief associated with the death of a loved one. Even more alarming, the immune system of caregivers whose loved one had died two years before remained less responsive to the body's invaders (i.e. viruses), making them less able to recover from stress. Future investigations should focus on ways to prevent the immune system from being compromised. These findings also underline the need for programs that can provide emotional support and physical relief to caregivers.

Depression in the elderly has been shown to be a chronic and relapsing problem. Elderly Americans have the highest rates of depressive symptoms among all age groups. Recent research on the treatment of consecutive episodes of major depression in elderly patients has generated valuable results. These NIMH grantees found that recurrent episodes of unipolar major depression can be successfully treated to remission in over 80 percent of the patients by using combined pharmacotherapy (nortriptyline) and interpersonal psychotherapy. These successful results were attributed to early intervention, rapid attainment of therapeutic levels of medication, and excellent compliance by the patients. The study shows that increased age does not necessarily imply diminished response or prolonged time to remission. It also shows that depressive disorder in the elderly appears to be as treatable as it is in younger patients. NIMH intends to strengthen geriatric psychopharmacology research to focus on strategies for reducing age-related side effects associated with psychoactive drugs. The Institute also plans to emphasize treatment trials of late life depression, paying special attention to the development of treatment strategies for very old patients as well as for those with complex physical, neurological, and psychiatric comorbidities.

Mental Health Services Research

NIMH was required by P.L. 102-321 to obligate from the amounts appropriated for a fiscal year not less than 15 percent to carry out health services research relating to mental health. Although this mandate was not binding on the Institute in FY 1995 while operating under Section 301, the Institute has, nonetheless, continued funding services research at this level. Services research focuses on a major challenge facing the Nation: how to provide effective care and services to the millions of Americans who suffer from mental illnesses. Caring for People with Severe Mental Disorders: A National Plan of Research to Improve Services (1991) has been a guide for a new research-based assault on the problems of service delivery. Based on recommendations of the plan, NIMH is funding:

- Studies of the economics of mental health. The purpose of this program is to stimulate applied economic research in mental health areas such as cost of illness, cost-effectiveness, health insurance, financing of services, payment mechanisms, and new methods of analyzing mental health services.

- Career development. The Institute is encouraging young investigators to pursue careers in developmental psychopathology, HIV/AIDS research, or mental health services research. NIMH is offering small dissertation grants to encourage and support doctoral candidates who are interested in research careers in one of these selected areas. The Small Grant (R03) mechanism will support up to 30 dissertation research grants for up to $25,000 per award each year.

- Centers. NIMH supports research centers that concentrate on mental health services for people of all ages. The intended outcome of these centers is to improve the quality, delivery, organization, effectiveness and financing of services to persons with mental disorders.

- Research on services for children. NIMH is encouraging research on the impact and effectiveness mental health services provided through the Center for Mental Health Services (CMHS) Comprehensive Community Mental Services Program to children, adolescents and their families. Research topic areas include but are not limited to: cost-effectiveness of intervention programs, clinical outcomes of comprehensive services, quality of care to children and families across different community settings.

One purpose of NIMH services research is to improve care for persons with severe and persistent mental illnesses. Recent results have shown that aftercare services and patient follow-up can benefit discharged mentally ill patients by improving their quality of life and reducing their clinical symptoms. These services include: discharge planning, referral to outpatient programs, set-up of appointments, and case management several months following discharge. Aftercare programs not only promote better patient functioning, they also make service provision more cost effective. For example, centralized and structured aftercare programs reduce the likelihood of rehospitalization limiting inpatient costs, as well as limiting duplicate services which reduces the costs to outpatient agencies. Despite the demonstrated benefits of these programs, an NIMH-sponsored national survey of mental health facilities reports that most mental health agencies provide little or no aftercare services. Only 26 percent of the respondents provided case management services. Thirty-five percent of those surveyed provided neither case management nor full-time follow-up staff. Most hospitals cite financial barriers as the reason for the lack of follow-up care. Further investigations will compare the initial costs of aftercare with the savings from reduced readmissions.

Prevention Research

Developing the knowledge necessary to prevent mental illness and promote mental health is a major goal of NIMH biomedical and behavioral research. Knowledge gained from mental disorder prevention research could also contribute to the prevention of other disorders whose etiology and course are intertwined with mental illnesses and their precursors. A growing number of studies suggest that mental disorder prevention programs may be particularly cost-effective and that successful interventions, introduced early, can help reduce the brutal burden of long term suffering. Current Institute programs focus particularly on the prevention of conduct disorder, which is characterized by disruptive behavior in school and at home. It is a childhood precursor to a variety of serious adult problems, including violence. Two recent landmark reports reviewed current prevention research and prepared separate, policy-oriented recommendations. The two reports, *The Prevention of Mental Disorders: A National Research Agenda* (NIMH Prevention Steering Committee, 1993) and *Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research* (the Institute of Medicine Committee on Prevention of Mental Disorders, 1994) together lay out an agenda for future prevention research. NIMH is producing a coordinated implementation program to address the recommendations in these reports and intends to fund research in support of these recommendations.

Health and Behavior

Scientists have traditionally described the brain and the immune system as two independent entities. However, NIMH research suggests that the brain and the immune system are in fact involved in a bidirectional communication network. Neuroimmune and neuroendocrine factors appear to mediate mental status and behavior, as well as health and disease. NIMH behavioral and neuroscience research is contributing to our understanding of compromised immunity in cancer, heart disease, diabetes, eating disorders, AIDS and many other diseases. Research is directed at determining whether the progression of these illnesses, especially in their early stages, can be modified by changes in mood and behavior. NIMH researchers have found suggestive evidence that behavioral interventions can improve immune system functioning. An NIMH study found that breast cancer patients who strengthened their coping skills through group psychotherapy increased their survival time in comparison to those patients not in therapy. NIMH believes that current efforts to develop more effective research tools and to create better experimental approaches will produce further breakthroughs in studies of brain/immune system interactions.

Aggressive and Violent Behaviors Research

Interpersonal violence has moved to center stage in national public policy as well as in communities across the nation. The Assistant Secretary for Health has recently identified it as the number one problem for the PHS to address. NIMH research examines the mental health aspects of aggression and traumatic stress, focusing on perpetrators of violence; victims; the legal system of criminal and civil commitment; and a program of emergency research, studying disaster, combat, community violence, and terrorism. Over 70 percent of the research that NIH conducts on violence and its consequences is funded by NIMH.

A landmark study funded by the NIMH has identified distinct personality types among batterers that could lead to more effective treatment programs for spouse abusers. The researchers have identified two personality patterns, impulsive and antisocial, that differ in motive for violence, physiology during arguments, and the level of emotional abuse inflicted upon the wives. Most violent husbands are considered impulsive batterers. During heated arguments they become increasingly agitated, their heart rates increase, and they eventually explode into violent behavior out of frustration. Jealousy and fear of abandonment is often the trigger for these intense arguments. Impulsive wife batterers use violence to prevent their wives from rejecting or abandoning them. In comparison, for antisocial spouse abusers the abuse is only part of a pattern of hostile and lawbreaking behavior. These violent men use insults, threats, and severe physical abuse to dominate their wives by instilling fear. As antisocial wife batterers become more hostile their heart rates fall and their attention sharpens, suggesting control rather than loss of control. For impulsive wife batterers, couples therapy designed to help the husbands manage their anger and control their aggressive impulses has been shown to be effective in reducing violent behaviors. This form of couples therapy has had less success with antisocial spouse abusers. Few effective interventions have been identified besides arrest for the husband and shelter and support for the wife. Future studies with antisocial spouse abusers may produce more promising results by making the character disorder the focus of intervention.

A common question concerning the causes of aggressive behavior is: Are people who are abused or exposed to marital violence in childhood more likely to become aggressive than those who do not have a history of violence? Studies involving intergenerational transmission of family violence shows that exposure to child abuse or marital violence is associated with an increased likelihood of aggression with one's own children. NIMH-funded investigators found that exposure to aggressive behavior is predictive of aggression across three generations for males and is predictive of both marital and parental aggression in the second generation. Child abuse potential in the second generation is predictive of aggression in the third generation males. NIMH research is continuing to study the patterns and precursors of violent behavior.

Women's Mental Health Issues

NIMH has a large portfolio of research focused on women's mental health and disorders. One area of research is eating disorders, anorexia nervosa and bulimia nervosa, which can be life-threatening. Recovery is slow and relapse is common. These disorders are estimated to affect less than 2 percent of adolescent girls and young women, but the prevalence of both disorders is increasing. NIMH is supporting research on the effectiveness of psychosocial and pharmacological treatments for eating disorders. The Institute, as part of its effort to disseminate sound, research-based information to both the public and the research field, is convening a Scientific Advisory Group on eating disorders with three broad goals: first, to organize existing research and establish a scientific consensus; second, to develop the content appropriate for a professional education campaign; and third, to establish messages appropriate for public education. NIMH also is actively collaborating with the DHHS/McKnight Foundation eating disorders education effort.

Recently, NIMH sponsored a meeting on the psychosocial aspects of reproductive dysfunction to bring together researchers on the cutting edge of this interface. Many aspects of reproduction seem to be associated with the development of mental disorders. For example:

- NIMH sponsors research on "premenstrual syndrome," generally used to refer to a cluster of mood and somatic symptoms that occurs regularly before the onset of menses and subsides once menses begins. Recently, the mood and behavioral aspects of this syndrome have been termed "late luteal phase dysphoric disorder (LLPDD)" on the basis of the development of operational criteria for its definition in the latest revision of the *Diagnostic and Statistical Manual, DSM-III-R.* Reproductive dysfunction (amenorrhea, irregular cycles, infertility, miscarriage, and stillbirth) also can be associated with mood and behavior changes and disorders. There is a commanding need for medication research and treatments for these disorders.

- With the development of new biomedical technologies, women now have greater control over the timing of reproduction. Psychosocial issues have arisen around the use of these procedures that have both positive and negative effects on women's mental health. Pregnancy-related and postpartum mental disorders, particularly affective disorders, occur in 10-15 percent of women. Little knowledge exists about the etiology, treatment, and prevention of mental illness during this period.

NIMH is cofunding a grant with the National Center for Human Genome Research that is comparing models of pre-test education for BRCA1 testing (a genetic test indicating the likelihood of developing breast cancer). Since genetic tests for cancer and other diseases are rapidly being developed, it is becoming increasingly important to determine the behavioral and psychological consequences of such testing and to develop counseling and educational methods for mitigating adverse consequences.

Rural Mental Health

NIMH continues to support research on rural problems through funding of three rural research centers. There are also three additional centers with primary foci on service provision or youth behavior in rural populations. Findings from this research are helping to direct the next generation of studies. For example, from a sample of 50 rural physicians in Arkansas, NIMH-funded researchers found that 44 percent of rural physicians consider medications alone enough for treating depression. The majority of rural primary care physicians prefer to treat depressed patients in their practices themselves. The greatest barriers to treatment were lack of time and patient resistance; the greatest barriers to referral were lack of mental health professionals, long waiting lists, or lack of provision for followup. Because of stigma, the physicians found it hard to ascribe a diagnosis of depression. These types of studies document that one of the serious difficulties in meeting mental health problems in rural America continues to be the lack of qualified mental health service providers and points to the difficulties in relying on the primary care sector as a solution.

Racially- and Ethnically-defined Populations

Results of an NIMH-supported study show that although black and white panic disorder patients do not differ in psychiatric symptoms, black patients with panic disorder show a higher incidence of isolated sleep paralysis. Lack of awareness of this culturally specific symptom has resulted in the missed diagnosis of panic disorder among black patients whose primary complaint is related to sleep paralysis rather than typical symptoms of panic disorder. Isolated sleep paralysis is an altered state of consciousness that occurs while falling asleep or awakening. Individuals report being unable to move for a few seconds or minutes and as a result experience feelings of anxiety or apprehension. Panic-like symptoms (i.e tachycardia, hyperventilation, fear) follow. Because this symptom of panic disorder is so rare among white patients, mental health professionals have not previously recognized its significance. These findings highlight the importance of research that investigates the unique cultural manifestations of mental disorders.

Asians Americans, including Pacific Islander Americans, are the fastest growing ethnic group in the United States. Their population has doubled every decade since 1970, and now is about 7.3 million people. The three largest groups are Chinese, Japanese, and Filipinos, followed by Asian Indians, Koreans, southeast Asians (e.g. Vietnamese, Cambodians, Laotians, and Hmong), and Pacific Islanders. An entire issue of the Journal of Community Psychology, was recently devoted to research results from the NIMH-supported National Center on Asian American Mental Health at the University of California at Los Angeles. The purposes of the issue were to yield insights into the culture, community, and experience of Asian Americans, to call attention to the within-group diversity of the Asian American community, to examine help-seeking behaviors and the use of mental health services by Asian Americans, and to evaluate the effects of culture-specific forms of treatment.

Research demonstrates that Asian Americans tend to underuse Western, mainstream mental health services. Contributing factors may be a level of shame and stigma associated with using such services, culturally biased views of mental health and disorder, and ignorance of the cultural and linguistic needs of Asian American clients. The research shows that Asian Americans avoid using services until the symptoms become very pronounced and the family or other forms of support are no longer able to assist. The researchers found that many Asian refugee groups combine mainstream mental health services with traditional practices from their homelands. Another study examined the mental well-being of Korean residents of Los Angeles following the April 29, 1992 riots, studying how culturally-based perceptions and social responses to the stressful riot events contributed to or detracted from the subsequent psychological and physical health reported by these people. In another study, adolescents from different cultural backgrounds, Asian-American, Mexican-American, African-American and Caucasian-American had better mental health outcomes when they received treatment from a therapist who spoke their language and had similar cultural experiences.

National Institute of Mental Health

Intramural Research

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
574	$84,466,000	599	$84,016,000	591	$86,419,000	-8	+$2,403,000

The NIMH Intramural Research Program (IRP) plans and administers a comprehensive long-term research program dealing with the causes, diagnosis, treatment, and prevention of mental disorders, as well as the genetic, developmental, environmental, and social factors that determine human behavior and development. The IRP operates laboratories and clinical branches on the campus of the National Institutes of Health, at the Poolesville Animal Facilities, and at the Neuropsychiatric Research Hospital on the campus of Saint Elizabeths Hospital in Washington, D.C. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year. The IRP scientists provide a critical link between basic and applied mental disorder research.

The IRP continues to develop its growing partnership with industry. Stimulated by the Federal Technology Transfer Act of 1986, the IRP scientists have had a steadily increasing number of collaborations with industry based on their inventions. At the beginning of FY 1995, fourteen Cooperative Research and Development Agreements (CRADAs) were active, and four new patents were filed from the six Employee Invention Reports (EIR) submitted. Also three new patents had been issued, bringing the total number of patents issued to NIMH investigators to forty-two.

Funding for Intramural Research during the last five years has been as follows:

	Amount	FTE
1991	$76,488,000	660
1992	84,564,000	680
1993	87,020,000	590
1994	84,466,000	574
1995	84,016,000	599

Rationale for the Budget Request

The FY 1996 request for Intramural research is $86,419,000, an increase of $2,403,000 over the FY 1995 level of $84,016,000.

Basic science is providing the fundamental knowledge base for mental illness research. Intramural investigators are world leaders in neurobehavioral and memory research, identifying new facets of the brain's malleability and neurological basis of learning and visual pathways, and utilizing the tools of molecular biology to study the effects of specific neurotransmitters, receptors, and second messenger systems on brain function.

Examples of some of the directions for research are:

- Schizophrenia, accelerating research on *in vivo* neuroimaging of brain functional neuroanatomy and neurotransmitter systems to reveal brain mechanisms involved in the etiology and treatment, as well as developing new pharmacologic interventions.
- Affective disorders, including alternatives to lithium in bipolar illness, using carbamazepine, valproate, nimodipine, and the neuropeptide TRH, and finding novel approaches to rapid cycling bipolar disorder through research on circadian rhythm disturbances.
- Anxiety disorders, continuing to define the role of brain neuropeptides in obsessive compulsive disorders (OCD) and further examination of and treatments for panic disorders.
- Mental illnesses of children and adolescents such as childhood schizophrenia and attention deficit hyperactivity disorder (ADHD) with emphasis on the progression from child to adult disorders, including further exploration of the relationship between antineuronal antibodies and OCD, Tourette's disorder, motor tics and choreas.
- Neuropsychiatric illness of the elderly with a three-fold approach--functional brain imaging, laboratory studies of cell biology, and clinical studies extending from pharmacologic modeling experiments with normal controls to treatment studies of geriatric depression and pilot drug studies with Alzheimer patients.
- Women's health, focusing on biological factors related to mood disorders, especially the finding that there appears to be a therapeutic role for estrogen because it is effective in the treatment of symptoms of perimenopausal depression in women. The goal of these clinical studies is the elucidation of the parts of the brain that may be abnormal in patients with mental health problems and the biochemical and structural changes that take place in these affected areas.

Complementing these studies is the genetic approach to finding causes of these diseases. Intensive efforts continue to be focused on the search for genetic abnormalities causing manic-depressive illness, schizophrenia, and other psychiatric disorders. Particular emphasis is placed on searching for DNA mutations in children with severe or early onset behavioral/psychiatric disorders and in discovering populations of patients that may prove especially informative.

National Institute of Mental Health

Research Management and Support

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
326	$30,675,000	298	$30,631,000	297	$31,224,000	-1	+$593,000

The Research Management and Support (RMS) activity at NIMH provides staff and resources for the administrative management and scientific direction of the Institute. The Office of the Director includes the administration and financial management programs of the Institute and the following organizational components: the Office of Equal Employment Opportunity, the Office of Legislative Analysis and Coordination, the Office of Scientific Information, the Office of Resource Management, and the Office of Program Planning and Science Policy. Other activities include the legislatively mandated Offices of: Special Populations, Prevention, Rural Mental Health Research, and AIDS. Scientific direction and administrative management of the Institute's extramural review and oversight is provided by the Division of Extramural Activities. This activity includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of their program's research grant, contract, and training programs.

Funding for the Research Management and Support program during the last five years has been as follows:

	Amount	FTE
1991	$27,507,000	338
1992	30,271,000	349
1993	31,980,000	358
1994	30,675,000	326
1995	30,631,000	298

Rationale for the Budget Request

The FY 1996 request for Research Management and Support is $31,224,000 and 297 FTEs. This represents an increases of $593,000 and a decrease of 1 FTE from the FY 1995 Appropriation of $30,631,000 and 298 FTEs.

P.L. 102-321 that reorganized the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and returned NIMH to the National Institutes of Health, mandated a number of requirements for NIMH. The law specified that the Institute was to obligate from the amounts appropriated for a fiscal year not less than 15 percent to carry out mental health services research. To meet this obligation, the Institute has increased management and oversight for this activity, in addition to that for those programs already being monitored due to Congressional interest, such as rural mental health, and Native American and Alaska Native mental health research funding. The law also established NIMH Associate Director level offices of Special Populations and Prevention; ratified the Offices of Rural Mental Health and AIDS; required development and implementation of new public education programs in the areas of suicide prevention, intervention, and treatment; stressed the necessity to address the needs of special populations including women's mental health issues; and entailed development of formal linkages and collaborative efforts with the Substance Abuse and Mental Health Services Administration (SAMHSA).

To comply with provisions in P.L. 102-321 and other Congressional mandates, the Institute has expanded its public education and prevention information dissemination programs, including information on suicide, eating disorders, and panic disorder. An ongoing initiative, the Depression: Awareness, Recognition, and Treatment (D/ART) program, is a public and professional education effort to reduce the prevalence of depressive disorders through early identification and effective treatment. Supported by RMS funds, D/ART uses a three-pronged approach:

- Professional training programs enhance the skills of primary care providers and mental health professionals in treating depression. Priority is given to geographical areas, particularly rural, that have not yet received funding, to developing other sources of funding for training primary care providers, and to extending medical school training programs to more sites.

- A public education campaign develops materials, provides them to the national media, and creates liaisons through a "Community and Professional Partnership Program." Public service announcements on television and radio and print materials are targeted for specific audiences. The "Partners" program brings together groups such as mental health agencies, the business community, and ethnic organizations, to provide depression-related educational activities in their local areas.

- A worksite program is designed to improve recognition of the toll depression takes in the workplace. The program conceived a multi-component, integrated approach to managing depression in the workplace.

Demand for NIMH-funded research results has led to a large increase in public and provider requests to the Federal Government's Consumer Information Center in Pueblo, Colorado. This Government clearing house distributes such NIMH pamphlets as You Are Not Alone, Alzheimer's Disease, and What To Do When A Friend Is Depressed, that are among the most frequently requested of **all publications** from the entire Federal Government. The Institute expects additional requests to the Center for information on Alzheimer's disease since President Reagan's announcement. New publications available since FY 1994 include: Anxiety Disorders, Attention Deficit Hyperactivity Disorder, Suicide Facts 1994, Mental Health and Rural America: 1980-1993, New Research Frontiers in Behavioral Medicine, Neuroimmunology and Mental Health, and a number of new materials on panic disorder.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	10	9	9
Office of Prevention	5	5	5
Office on Equal Employment Opportunity	2	2	2
Office of Rural Mental Health Research	2	2	2
Office for Special Populations	5	5	5
Office on AIDS	10	9	9
Office of Legislative Analysis and Coordination	5	4	4
Office of Scientific Information	23	21	21
Office of Resource Management	69	63	63
Office of Science Policy and Program Planning	10	9	9
Division of Neuroscience and Behavioral Science	32	29	29
Division of Clinical and Treatment Research	52	48	48
Division of Epidemiology and Services Research	54	49	48
Division of Extramural Activities	47	43	43
Division of Intramural Research Programs	574	599	591
Total	900	897	888

	Average GM/GS Grade
1991	10.3
1992	10.2
1993	10.2
1994	10.2
1995	10.2
1996	10.2

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

National Institute of Mental Health

Program Administration

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-6	2	3	2
ES-5	2	3	3
ES-4	11	11	10
ES-3	2	2	2
ES-2	1	1	1
Subtotal	18	20	18
Total - ES Salary	1,936,300	2,151,444	1,936,300
GS/GM-15	56	54	53
GS/GM-14	86	85	83
GS/GM-13	76	75	75
GS-12	72	72	71
GS-11	92	92	92
GS-10	1	1	1
GS-9	78	78	78
GS-8	37	37	37
GS-7	130	130	128
GS-6	36	36	36
GS-5	14	14	14
GS-4	7	7	7
GS-3	1	1	1
Subtotal	686	682	676
Total - GS/GM Salary	30,394,097	30,945,099	31,660,520
Grades established by Act of July 1, 1944 (42 U.S.C 207):			
Assistant Surgeon General	1	1	1
Director Grade	26	25	24
Senior Grade	15	16	16
Full Grade	13	13	13
Senior Assistant Grade	2	2	2
Assistant Grade	0	0	0
Subtotal	57	57	56
Ungraded	138	138	138
Total permanent positions	195	195	194
Total positions, end of year	899	897	888
Total full-time equivalent (FTE) employment, end of year	900	897	888
Average ES level	4.0	4.0	4.0
Average ES salary	107,572	109,594	112,241
Average GS/GM grade	10.2	10.2	10.2
Average GS/GM salary	44,306	44,874	45,958

WEDNESDAY, MARCH 22, 1995.

NATIONAL INSTITUTE ON DRUG ABUSE

WITNESSES

DR. ALAN I. LESHNER, DIRECTOR
RICHARD A. MILLSTEIN, DEPUTY DIRECTOR
DONNA M. JONES, BUDGET OFFICER
DR. KIRSCHSTEIN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. BONILLA [presiding]. The subcommittee will come back to order. And we are going to hear from Dr. Alan Leshner from the National Institute on Drug Abuse. Doctor, we would be delighted to hear from you at this time.

INTRODUCTION OF WITNESSES

Dr. LESHNER. Good afternoon, Mr. Bonilla. If I could introduce the people who are with me. Dr. Kirschstein, the Deputy Director of NIH, Mr. Beldon, from the Department, Richard Millstein, the Deputy Director of NIDA, Donna Jones, who's our Budget Officer.

OPENING STATEMENT

Thank you. I'm pleased to come before you and have the opportunity to highlight some of NIDA's recent accomplishments and our priorities for the coming year. The National Institute on Drug Abuse has the unique distinction of being the major entity in the entire world charged with bringing the incredible power of biomedical science to bear on drug abuse and addiction. In fact, NIDA supports nearly 85 percent of the entire world's biomedical and behavioral research in this arena.

Drug abuse and addiction are unquestionably among the most complex and far-reaching health and social problems, and it touches virtually every individual and family in this country, either directly or indirectly. And with your support, we're making excellent progress. NIDA's scientific research more and more shows drug use to be a preventable behavior and addiction to be a treatable although chronic and relapsing disease of the brain.

One of the most exciting and important accomplishments is that we at last have the scientific base from which to develop far more effective treatment and prevention strategies. Among our field's most significant discoveries has been the molecular cloning of the brain's receptors for virtually every drug of abuse. And this is not just an interesting scientific fact. In the past year, NIDA researchers have used this information to move beyond cloning, to begin to understand the cellular and genetic bases of addiction, and to develop therapies that are based in fact on that basic science understanding.

These discoveries are particularly hopeful in cocaine research. I've said in a variety of settings that the single most important need in the battle against drug use and addiction is an anti-cocaine medication of which we now have none. However, we at last have a science base from which to strategically develop effective pharmacological treatments for cocaine addiction. We've declared the development of an anti-cocaine medication as NIDA's top priority, and we have over a dozen candidate compounds in various stages of medication development and testing.

In addition, for fiscal year 1996 we will expand our efforts toward developing more effective pharmacotherapies and medication regimens for women, including particularly pregnant women. We recently reported that over 225,000 babies are born every year to mothers who abused illicit drugs during their pregnancy. We must have medications to treat these women without further harming their babies.

NIDA supported research is also making important contributions to reducing the spread of AIDS. Our studies have demonstrated that drug abuse outreach and intervention programs are highly effective in changing behaviors associated with the spread of HIV and AIDS, even among active drug users. This is critical in light of recent CDC findings which show that three in eight cases of AIDS are now related to injection drug use.

In fact, drug abuse is now the fastest-growing vector for the spread of HIV. This is of major significance, not only to the drug-abusing population, but to their sexual contacts and to their children as well. Indeed, 55 percent of pediatric AIDS cases are among children born to mothers who themselves injected drugs or had sexual contact with an injecting drug user.

The chronicity of drug addiction and its complex social and behavioral correlates make it imperative that NIDA continue its effort to better understand the behaviors underlying drug use, and then to use that understanding to develop better strategies for treating and preventing drug addiction. Already existing effective treatments can, when implemented properly, not only reduce personal and societal suffering, but also save billions of dollars by reducing not only drug use, but reducing crime and violence and the need for health and social services as well.

Conservative estimates show that for every one dollar invested in addiction treatment programs, there is a return of between four and seven dollars in reduced drug related crime, criminal justice costs and theft alone. Better treatments identified through research have potential for even greater savings. And NIDA supported research is improving treatment all the time.

For example, studies at our intramural research program in Baltimore have shown that personality characteristics like antisocial personality disorder, are excellent predictors of who will and who will not respond to a range of behavioral treatment approaches. The more we learn about what treatments work for whom and under what circumstances, the greater our chances of breaking the cycle of addiction that afflicts so many individuals and their families, often for generations.

NIDA supported research is explicitly directed at these treatment matching issues. In addition, NIDA's behavioral therapies development initiative is building upon knowledge gained from basic behavioral and clinical studies, to better define the process of addiction and to develop more effective behavioral interventions.

We've declared NIDA's year 2000 goal to be to have science replace ideology as the foundation for drug abuse prevention, treatment and policy strategies. Scientific research has clearly identified drug abuse as a preventable behavior, and addiction as a treatable disease, with both biological and behavioral components. There remains a public perception that addiction is purely a social problem to be dealt with only through social programs or only through the criminal justice system. This misperception is not only counter to scientific fact, but it is counterproductive to long term solutions for our Nation's problem. Accordingly, NIDA will expand its effort to educate the public, the treatment community and policy makers about the true nature and health consequences of drug addiction.

To accomplish its goals, NIDA requests $298,788,000 for fiscal year 1996.

I'll be pleased to answer any questions.

[The prepared statement and biography of Dr. Alan Leshner follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of The Director
National Institute on Drug Abuse

Mr. Chairman and members of the Subcommittee, I am pleased to come before you again as Director of The National Institute on Drug Abuse and to review our scientific advances and plans for the coming year. During my first year, I have seen NIDA's principal mission of bringing the power of science to bear on drug abuse and addiction carried out in many exciting and innovative ways. As I conclude my first year, I am struck by the extraordinary quality and depth of NIDA's scientific research. This research continues to demonstrate what we have known for many years, that drug abuse is a preventable behavior and addiction is a treatable disease of the brain. One of the things that I find most exciting, is that right now we have the scientific base to understand the neurobiology of addiction and to develop effective treatments based on scientific discovery. This makes it even more imperative that we bridge the gulf between public perception of drug addiction as a moral failing and what we know from scientific inquiry, that it is a treatable biologically based disease.

The scientific advances of the past year have continued to build upon the advances in drug abuse research of the past decade in furthering our understanding of drug addiction. Drug abuse researchers are making significant discoveries at an unprecedented rate, while spectacular advances in technology are opening even more avenues of research.

Among the most exciting and significant discoveries of the past decade was the molecular cloning of the receptor genes for virtually all drugs of abuse. In the past year, NIDA researchers have used this information to move beyond cloning to begin to understand the molecular and genetic basis of addiction and develop gene-based therapies. For example, cloning of the genes for the brain sites at which drugs act has allowed for the development of models to study the molecular biological basis for tolerance and dependence. These and other studies are presenting us with unprecedented opportunities to determine the molecular and cellular mechanisms of tolerance, dependence, sensitization, craving and withdrawal. A greater understanding of these mechanisms could then facilitate the development of treatments, such as replacement therapies, for the various aspects of addiction.

In particular, these discoveries have propelled us dramatically forward in cocaine research. One of the sites where cocaine acts in the brain has now been identified; its molecular structure has been determined; the specific segment of the molecule that binds cocaine has been identified; and the gene for the molecule has been cloned. We have gained a greater understanding of how cocaine interacts with neurotransmitter systems in the brain and we have mapped certain biological effects of cocaine to specific sites on chromosomes. These findings are providing the foundation of our understanding of how cocaine acts in the brain. We are now ready to use this information to develop effective pharmacological treatments for treating cocaine addiction.

NIDA researchers have also made exciting advances in our studies of opiate addiction. We have developed a cell model for studying specifically how opiate's, such as heroin, act in the brain. We have also shown that more effective analgesia with fewer side-effects can be obtained by either causing local release of endogenous opioid peptides or by using a novel drug delivery system that enhances the amount of opiates that reach the spinal cord. Each of these discoveries, along with the many others, are providing us with the scientific underpinnings from which we can better understand and treat opiate addiction. They are also opening up a new field of pain research and may eventually lead to the discovery of a non-addicting analgesic with fewer undesirable side effects.

In another domain, NIDA research has also demonstrated that drug abuse outreach and intervention programs are highly effective in reducing behaviors associated with the spread of HIV/AIDS. The development of these types of programs is critical in light of recent CDC findings which show that as of June 1994, 3 out of every 8 cases of AIDS were related to injection drug use. In fact, drug abuse is currently the fastest growing vector for the spread of HIV, not only among drug users, but also among nondrug using populations. This is of critical impact not only to the drug abusing population, but to their sexual contacts and to their children. Indeed, 55% of pediatric AIDS cases are among children born to mothers who had been injecting drugs or had sexual contact with an injecting drug user.

NIDA research has now determined specific factors that should be present in intervention programs aimed at reducing the spread of HIV among youth and we have begun to identify the most effective types of interventions appropriate for different groups and communities. NIDA is also assessing the interaction between drug use, the immune system, and the transmission, development and progression of HIV/AIDS, and drug abuse treatment as a strategy for preventing the spread of HIV.

NIDA researchers have also been identifying the effect of abused drugs on the progression of AIDS. For example, there is evidence that opiates, such as heroin, may suppress immune functioning, which may lead to a more rapid disease progression in HIV positive drug abusers. Additionally, both cocaine and alcohol have been found to inhibit the functioning of immune cells that are important for cell-mediated immunity and that are the primary target of the HIV virus. These types of studies are providing fundamental information that could lead to an increased understanding of the HIV virus, as well as strategies to reduce the spread of HIV among and by injection drug users.

One of NIDA's top priorities continues to be the development of effective pharmacological treatments for drug addiction. Following the 1993 FDA regulatory approval of the anti-opiate medication LAAM, NIDA has been working extensively with the Center for Substance Abuse Treatment to provide State authorities with the information they need for its introduction. These efforts have resulted in the effective use of LAAM in over half of the United States and progress towards its use in many other states. We now have declared the development of a cocaine medication our top priority. The science base for such a medication is there and we should take advantage of this opportunity.

Previous research has shown that treatment can work and that for every $1 invested in treatment programs there is an average return of $7 in reduced drug-related crime, criminal justice costs and theft alone [California Drug and Alcohol Treatment Assessment (CALDATA) study, July 1994]. Among the most successful forms of treatment are those based on behavioral approaches. In the past year, NIDA has continued to identify the most effective treatment modalities and to match patients with treatment modalities to improve treatment outcomes. A variety of behavioral interventions have now been documented as being more effective than "standard" care. Highly structured, multi-component, outpatient "relapse prevention" regimens have been developed and documented to be effective by NIDA researchers, as have comprehensive interventions to help addicts make the initial transition to abstinence.

Other findings from multidisciplinary teams are providing an informed basis for the strategic, rational development of behavioral therapies. For example, NIDA researchers have begun to separate the behavioral phenomena of craving from drug seeking. These data can help us to understand the mechanism of craving and how it relates or does not relate to drug seeking behavior. This is significant in that it refutes the long-held belief that drug seeking is only a response to craving, and opens the way for targeted treatment interventions.

NIDA health services research has identified factors that may lead to better outreach, improved treatment retention, and better treatment outcome. For example, case management for injection drug users was found to improve treatment access, entry, and retention, which resulted in reduced opiate and cocaine use. Another study found that enrolling patients in a mobile health care/methadone service was successful in reaching hard-to-treat clientele.

During the past year, NIDA researchers have also continued to identify factors that put individuals at risk for drug use, as well as factors that may protect an individual from vulnerability to drug abuse. Studies show that many of the factors that can result in drug abusing behaviors can be identified early in individuals who are at high-risk for drug abuse, making prevention possible. NIDA researchers have also found that non-escalating, occasional drug use often results from social, situational, and environmental factors, but drug abuse in higher quantities and frequencies often results more from biological, psychological, and psychiatric factors. These studies are helping in the development of more effective prevention and intervention strategies among all groups, including children.

The tremendous advances of the last few years in our understanding of addiction as a brain disorder coupled with the exciting, new technological advances, such as brain imaging and gene cloning, now set the stage for detailed molecular and cellular studies exploring the mechanisms underlying complex and clinically important behaviors relevant to drug abuse. As we approach the twenty-first century, it is critical that we take advantage of the opportunities now available by continuing to support research in promising areas.

Neuroscience and molecular biology are two of the most exciting and promising areas in which NIDA is taking advantage of currently available opportunities. Drug abuse research needs to continue to move beyond cloning to sophisticated, investigations of the relationships among protein function and behavior, and how drugs of abuse affect those relationships. As the field of drug abuse research moves beyond cloning, it is also important that NIDA encourage and foster multidisciplinary approaches, particularly in the behavioral and imaging areas, to enhance understanding of the consequences resulting from molecular manipulations and we are doing that.

Through the use of advanced technologies, NIDA now has the opportunity to use the power of science to better understand all aspects of drug addiction. For example, it is now possible to gain insight into the neurobiological basis for drug craving, sensitization, withdrawal and relapse, including the role of conditioned behaviors and stimuli. It is also now possible to investigate the specific brain mechanisms underlying the positive reinforcing properties of a drug, as well as the neurobiological consequences of chronic drug use. We can now use advanced imaging techniques to define the neuroanatomical and neuropharmacological basis for virtually every behavior associated with drug use.

Through the use of integrated approaches, and by taking advantage of the opportunities now available, NIDA can dramatically increase its understanding of the neurobiology of addiction, which could ultimately lead to new therapeutic and prevention strategies of direct relevance and application to the public health problem of drug abuse.

It is imperative that NIDA take advantage of the tremendous science base provided by years of research to develop a much needed medication to treat cocaine and crack addiction. In fact, our current major emphasis is the development of an anti-cocaine medication. Dramatic discoveries of the last few years have provided critical details as to the actions of cocaine in the brain. These research advances are making it possible to design medications based on the structure and activity of the cocaine binding molecule in the brain. As we continue to gain an increased insight into how cocaine's effects are mediated in the brain, the possibility of developing an effective pharmacotherapy increases dramatically.

NIDA is also working strategically toward providing pharmacotherapies for women, particularly pregnant women. We anticipate substantial progress in the identification of medications and dosing regimens that can be safely used by pregnant women. As new pharmacotherapies are developed or identified the safety and efficacy of these therapies for women will be determined.

At the same time that our scientists are making significant advances, a dramatic increase in marijuana use among high school seniors has been reported by the 1994 Monitoring the Future study. In response to this, NIDA has devised a research agenda aimed at augmenting the knowledge base that has been established over two decades of research. The focus of this research is on a more indepth investigation of the factors associated with the changing trends in drug use, the characteristics of those using drugs, the processes and mechanisms underlying the initiation and progression of drug use, and the acute and chronic consequences of drug use. We are coupling these efforts with an aggressive public information campaign designed to educate and prevent marijuana use.

The chronicity of the illness of drug addiction and the complex social and behavioral correlates make it imperative that NIDA continue in its efforts to understand the behaviors underlying drug abuse and addiction and to develop strategies for treating and preventing drug addiction based on this understanding. NIDA's Behavioral Therapies Development Program builds upon knowledge gained from basic behavioral and clinical studies to define the process of addiction in humans and develop more effective behavioral interventions.

NIDA will continue to conduct research into the many other aspects of drug abuse and addiction. For example, NIDA research will assess the effectiveness of drug prevention efforts in primary health care settings, target culturally diverse groups for prevention programs, develop more effective approaches for rural areas, and identify those components of prevention programs that seem to have the greatest impact in different population subgroups, developmental stages, and environmental settings.

Finally, NIDA has a goal for the turn of the century to have science replace ideology as the foundation of drug abuse and addiction prevention, treatment and policy strategies. Although scientific research has clearly identified drug addiction as a treatable disease with a biological basis, there remains what I have been calling the unique disconnect between what NIDA's research has shown and what too much of the general public thinks about drug abuse and addiction. Drug addiction is all too frequently viewed only as a social problem, to be dealt with only through social programs or through the criminal justice system. Moreover, drug addicts are too often seen simply as weak or bad people and, therefore, not deserving of care and treatment. Science, on the other hand, has taught us that, while the initial act of drug taking is voluntary, drug addiction is a chronic, relapsing disease of the brain. The difference between the perception of a "bad person" vs a "chronic illness sufferer" has tremendous implications. If we are to be successful in intervening with the consequences of drug addiction, it is crucial that the current myth-based perceptions be replaced with scientifically based facts. Accordingly, NIDA will expand its efforts to educate the public, the treatment community, and policy makers about the true basis of drug addiction.

Thank you Mr. Chairman. The FY 1996 budget request for NIDA is $298,738,000. I would be pleased to answer any questions.

ALAN I. LESHNER

Director
National Institute on Drug Abuse
National Institutes of Health

Dr. Leshner was appointed Director of the National Institute on Drug Abuse (NIDA) in February 1994. As NIDA Director, he is responsible for leading the nation's efforts to bring the power of science to bear on drug abuse and addiction. NIDA both supports and conducts research in a wide range of disciplines, and it carries out a large variety of programs to ensure the rapid dissemination and use in both practice and policy settings of the results of the research it supports.

Prior to coming to NIDA, Dr. Leshner had been the Deputy Director of the National Institute of Mental Health since 1988. He also served as Acting Director of the NIMH from 1990 to 1992. Among his major accomplishments at NIMH were a major restructuring and enhancement of treatment research, and the development of the Human Brain Project. He was appointed by the Secretaries of HHS and HUD as Chair of the task force that produced Outcasts on Main Street, which lays out a blueprint for substantially reforming the national system of care for homeless persons with severe mental illnesses and substance abuse.

Dr. Leshner went to NIMH from the National Science Foundation (NSF), where he held a variety of senior positions, focusing on basic research in the biological, behavioral and social sciences, and on science education.

Dr. Leshner went to NSF after 10 years at Bucknell University, where he was Professor of Psychology. While on the faculty at Bucknell, he also held long-term visiting appointments at the Postgraduate Medical School in Budapest, Hungary, at the Wisconsin Regional Primate Research Center of the University of Wisconsin, and as a Fulbright Scholar at the Weizmann Institute of Science in Israel. Dr. Leshner's research has focused on the biological bases of behavior. He is the author of a major textbook on the relationship between hormones and behavior, and numerous book chapters and papers in professional journals. He also has published extensively in the areas of science and technology policy and education.

Dr. Leshner received his undergraduate degree in psychology from Franklin and Marshall College, and the M.S. and Ph. D. degrees in physiological psychology from Rutgers University. He has been elected a Fellow of the American Association for the Advancement of Science, the American Psychological Association, the American Psychological Society, and the New York Academy of Sciences. He has received awards for his national leadership from such diverse groups as the American Psychiatric Association, the National Alliance for the Mentally Ill, the American Psychological Association, the American Academy of Child and Adolescent Psychiatry, the National Mental Health Association, and the National Prevention Coalition.

NATURE OF ADDICTION

Mr. BONILLA. Doctor, how hard has it been to sell the public on the fact that prevention is important and social solutions are not the only solutions to someone who's afflicted with drug addiction?

Dr. LESHNER. As a public health official, this has been the single biggest problem that I have. I call it the great disconnect. It is the public perception that drug abuse and addiction are simply a social problem. To the contrary, we in the health professions understand through research that, in fact, drug addiction is a disease of the brain; drug use is a preventable behavior, voluntary as it may be.

And that disconnect is a terrible problem. So we've been working in a variety of forums in order to try to educate the public about that bridge. One manifestation of the problem is in getting people into treatment; they don't understand that drug addiction is in fact a treatable disease, and that in fact we've made tremendous progress, and that we can bring people back to being productive members of society. It is truly a major problem.

Mr. BONILLA. Is there a level of addiction? Obviously, sometimes things start slowly and you're not a hard core addict from day one in many cases. Is there a point at which you reach the point of no return where it is not a social solution any more? Could it be a social solution when it's just starting out?

Dr. LESHNER. I think there is no question that initial drug use is a voluntary behavior. And I think everyone would agree with that point. However, for many, many people, only initial drug use is a voluntary behavior. And I would say, not to sound glib, that addiction is not just a lot of drug use. We believe addiction to be a change in the structure and the functioning of the brain. And I could give you a large amount of scientific evidence to show that. Vulnerability varies from individual to individual, but at some point, voluntary drug use turns into addiction and becomes a totally different, qualitatively different phenomenon. We've been studying the brain mechanisms involved in that process and have a lot of insight.

Nevertheless, when we see the initial voluntary drug use, it's not a simple problem. It's not just an issue of changing global social factors. It seems to be a much more directed, focused kind of effort about, for example, purveying actual, reliable, credible and factual scientific information about the nature of drug use. It's a very complex process. There are no simple solutions. Certainly we have learned over time that criminal justice solutions are not the only solutions.

DRUG ABUSE IN RURAL AREAS

Mr. BONILLA. It used to be, at least the perception was that major drug abuse problems were primarily in urban areas. Are you seeing it spread into rural areas these days?

Dr. LESHNER. That's a very interesting question. We've seen a very interesting trend over the years. In the late 1970s, when some drug use peaked, and then in the mid 1980s, when the crack cocaine epidemic peaked, there were tremendous differences between drug use levels in urban areas and rural areas.

What's happened, however, is that as drug use has decreased through the 1980s in urban areas, it's become steady or actually increased a bit in rural areas. In response, we have mounted a major joint program with the U.S. Department of Agriculture to begin to look at what are the unique problems in rural areas, and how we can do a better job of both monitoring what's going on there, because it's hard to know what's happening, and, in addition to that, developing appropriate prevention and treatment strategies.

Mr. BONILLA. I didn't quite understand, what is closing the gap now?

Dr. LESHNER. The gap's closing in two ways. One way is that we believe that there is a rise in drug use, and certainly drug availability, in rural areas. And there had been a drop in drug use during the 1980s in some metropolitan areas. As drug use went down in some areas, it did not go down in rural areas. Therefore, the rural areas are coming up a little bit, and the urban areas had gone down, although they are now beginning to rise again as well.

So there had not been the decrease in drug use for the rural areas that had been seen in urban areas.

Mr. BONILLA. I'll turn it back over to Chairman Porter.

I have some lengthy questions for you that I will submit for the record, and if you could get back to me on that, I would appreciate it.

Dr. LESHNER. My pleasure. Thank you, sir.

Mr. BONILLA. Thank you.

NEEDLE EXCHANGE

Mr. PORTER [resuming]. Use of needle exchange, Dr. Leshner, it is seen as a way to control the spread of AIDS. It's been very controversial. I wonder if you can summarize the research findings on needle exchange, and its impact on AIDS prevention and drug usage.

Dr. LESHNER. The issue of needle exchange has been an extremely controversial issue, and it's one of those things where a scientific institute hopefully can be useful in providing clear factual scientific information to inform the policy debate.

However, I'm sorry to say that we don't have an answer to that yet. We do have six research grants ongoing, evaluating needle exchange programs around the country, examining needle exchange as a strategy for preventing the spread of HIV and AIDS, but we don't yet have the findings of those studies. So although there is anecdotal evidence that goes in both directions about the effectiveness of needle exchange and the ineffectiveness of needle exchange, we have not yet completed those studies. So I can't give you a definitive answer.

In addition to that, the National Academy of Sciences is in the midst of a major study looking at experience in the literature around the country on this issue. So we hope we'll have an answer for you within the next couple of years. But we do have studies systematically looking at this issue, for precisely the reason that I laid out, which is to try to have a scientific base to inform the debate.

MEDICATIONS DEVELOPMENT

Mr. PORTER. Sorry for the interruption.

You state in your testimony that development of a drug to counteract the effects of cocaine is now a major priority for your Institute. Haven't you been working on this since the mid 1980s, when crack cocaine first came on the scene?

Dr. LESHNER. People have been looking for what I would call a molecular marker at which to target the development of a cocaine medication for a long time. As an Institute, we actually only began our systematic medications development program in the early 1990s—1990 and 1991.

We believe that we now have enough information about the way in which cocaine affects the brain, the way in which it produces its high, the way in which it produces craving, that we have a series of strategies that we're using to build on that science base and do what I call rational, systematic medication development. We have about 12 compounds in various stages of testing, and we're using again, a variety of molecular markers as a way to target those medications, to screen drug libraries that we're getting from drug companies, for example, or to use other approaches.

It is only with the cloning of the receptors in the brain for cocaine and the discovery that cocaine and dopamine (the major neurochemical affected by cocaine) are not working on the same precise sites on the receptor, that we now have real hope that we can develop a medication for cocaine addiction. But we are there, and we're moving as quickly as we can in order to provide that badly needed help.

Mr. PORTER. Can you describe for which drugs of addiction some form of pharmacological therapy applies?

Dr. LESHNER. At the moment, we only have what I would call effective pharmacological treatments for heroin addiction. We have methadone. The National Institute on Drug Abuse was successful in the last few years in working with the FDA to provide LAAM, a new treatment for heroin addiction.

We have in trials now a compound called buprenorphine, which we're hopeful also will be useful in treatment. And, of course, we have naloxone, for the treatment of heroin overdose, and we have naltrexone, which is also used as a treatment for alcohol abuse, but was originally developed as a treatment for heroin addiction.

We have in addition, of course, a wide range of behavioral treatment modalities that are useful for all kinds of drug abuse. But in the case of medications, per se, our only real medications at the moment are for heroin addiction.

ADOLESCENT DRUG USE

Mr. PORTER. You mentioned the upturn in marijuana use among youths. This may not be a fair question, but does this indicate that research has not developed effective prevention techniques, or that programs such as the $482 million drug-free schools program are not translating those techniques effectively?

Dr. LESHNER. Very difficult question. The issue of preventing drug use has to be one of the most complex issues on both a social level and an individual level in the country. There are over 70 risk factors for drug abuse that have been identified at the individual level, family level, the group level, the community level, the societal level. And we're beginning to understand protective factors that protect kids from drug use or developing drug use. And we've had to hone our prevention strategies over time.

We know that drug prevention programs in the schools can be a highly effective technique for preventing drug use in some children. By themselves, they don't work as well as when they're combined with a number of other prevention modalities, media campaigns, and community efforts.

But we don't know a tremendous amount, obviously, or we would have done better at it. We don't know a tremendous amount about exactly how to go about preventing drug use. But we do have, in our case, a large research portfolio looking at a variety of behavior change strategies, looking at strategies targeted particularly at the prevention of drug use. A great deal is known, but a great deal more needs to be known.

CLINICAL RESEARCH ON DRUG ADDICTION TREATMENT

Mr. PORTER. Last year, you indicated that few researchers in the extramural community were interested in conducting clinical research on drug addiction treatment. Has this situation improved at all?

Dr. LESHNER. A little. We have mounted a major clinical research infrastructure development program. I have a special assistant for medical affairs who is a psychiatrist whose job it is to help us build that clinical research infrastructure. We have sent out NIDA staff to visit a number of drug abuse clinical research settings and neighboring ones. We've been working with the professional societies in an attempt to help build the clinical research infrastructure that we need so badly. We're using our training grants in that way, and a variety of the other mechanisms. But we haven't accomplished it yet. One year may be too quick.

FETAL AND CHILD DEVELOPMENT

Mr. PORTER. You're supporting a study of the effects of prenatal drug exposure in the first three years of life. Do you have any feeling for the study's findings at this point?

Dr. LESHNER. We have a large number of studies, of course, on the interaction between maternal drug use and the effects on infants. In addition, we have a series of collaborations with other NIH Institutes, like the National Institute of Child Health and Human Development.

We know, actually, a fair amount about the devastating effects of, for example, cocaine use during pregnancy on the development of the fetus and the development of young children. It relates to retarded growth and reduced infant body weight, motor impairments, and of course crack-exposed babies are born addicted to cocaine. We're working hard to try to understand the mechanisms and the prevention strategies and the treatment strategies, but we don't have definitive results yet of that particular study.

Mr. PORTER. We don't hear as much about crack babies as we used to. Is that because they've been replaced in the public's mind or the media's approach with HIV-infected babies, or are the developmental deficits less severe than we thought?

Dr. LESHNER. Our understanding is that the initial developmental deficits are extremely severe. It appears that some children recover following treatment and are able to develop well in spite of that early childhood trauma. Other babies do very poorly.

There's a certain amount of plasticity in the brain, of course, and an ability to recover from that kind of an early traumatic experience. But I would not want to imply at all that the problem is not tremendously severe. These children who are crack-exposed babies are not just born to drug abusing parents, but they are raised by drug abusing parents. They are subject to all of the social and environmental influences of being a part of that drug culture. And they suffer from all of those other deficits, so that the problems go way beyond just the pharmacologic effects of having been exposed to crack early in life.

Mr. PORTER. Are there more cocaine-addicted babies than there were five years ago, say?

Dr. LESHNER. We don't know that. The crack epidemic has leveled off in a very large number of sectors, but I don't think that there are fewer or that there are significantly more. I do know that the epidemic has leveled off at about 2.7 million hard-core users of drugs, mostly cocaine.

Mr. PORTER. And the costs, of course, of medical care for those babies is huge to society. And if there is something we can do, either through behavioral change or through, well, prevention or perhaps some medical way to short-circuit the effects on the child, it would save a lot of money.

Dr. LESHNER. Absolutely.

Mr. PORTER. As well as human misery.

Dr. LESHNER. There have been numerous studies on the cost-effectiveness of drug treatment. And there is a tremendous body of literature that shows the cost savings in all spheres from drug treatment approach, and everything we do to improve treatment, of course, is helpful.

Mr. PORTER. Mr. Stokes.

DRUG ABUSE PREVALENCE

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Leshner, always a pleasure to see you.

Dr. LESHNER. Nice to see you, sir.

Mr. STOKES. Thank you.

Doctor, how extensive a problem is drug abuse in the United States population? And tell us, how does the extent of that problem compare with that of other countries?

Dr. LESHNER. Well, the United States has somewhere on the order of 77 million individuals who have used an illicit drug at some time in their life. That's approximately 30 percent of the population. That's a tremendous problem. There are 2.7 million hard core drug users, of which somewhere on the order of 500,000 to 700,000 are heroin addicts and the rest are cocaine addicts. We have a tremendous drug problem in this country, and it is not getting better yet.

Our drug abuse problems are greater than some countries' and lesser than other countries'. But we do have a relatively very, very serious drug problem, public health problem, indeed.

DRUG ABUSE AMONG YOUTH

Mr. STOKES. In terms of our youth population, does your Institute have activities underway to address abuse in high school students or youth in general in that age range?

Dr. LESHNER. Absolutely. We particularly, since I came to NIDA, have declared children and adolescents as our major priority target. We believe that drug abuse is the largest ruiner of young peoples' lives, the most costly and deadly long-term thing that can happen to a child. We have a series of activities that are both of a research nature and of a public information nature that are targeted specifically at children and adolescents. You may be familiar with our "Get High, Get Stupid, Get AIDS" campaign, which has received a tremendous amount of publicity and visibility. Keep your eyes open, we're about to come out with a new edition.

You may know that Secretary Shalala recently announced a major anti-marijuana prevention campaign that the National Institute on Drug Abuse will be leading. We do it in partnership with the Partnership for a Drug Free America, and the Center for Substance Abuse Prevention. We are devoting a large percentage of our portfolio to studying the particular problems of children and adolescents, both in terms of prevention issues and in terms of treatment issues, as well, of course, as the issues of identifying what the major risk factors are.

Mr. STOKES. When we use the term drug abuse as it relates to youth, how extensive a problem is it?

Dr. LESHNER. Well, as you know, just to give you an idea, we put out the high school survey every year. And you may recall that this year we reported a significant increase in illicit drug use in 10th graders, 12th graders, and, most frighteningly, in 8th graders. A tremendous percentage of students have used some illicit drug at some time; for example, 38.2 percent of high school seniors have used marijuana at some time in their lives. Cocaine use, lifetime again, for 10th graders, was 4.3 percent. Very frightening.

Mr. STOKES. Cocaine?

Dr. LESHNER. Cocaine. Three point six percent of 8th graders have used cocaine some time in their life. The number of users is rising and that is one of the major reasons why the Secretary has chosen to mount this major prevention campaign directed at youngsters.

Mr. STOKES. Now, you've mentioned marijuana, and you've mentioned cocaine. Are there any other drugs that they abuse?

Dr. LESHNER. We have a terrible problem, of course, with even heroin use in high school kids, although a number of heroin addicts become addicts later in life. We have problems with methylphenidate, ritalin, hallucinogens of all kinds.

Again, the numbers are creeping up in middle school and high school for the use of LSD and PCP. It's a very serious problem among adolescents. The cost effectiveness of this issue is important too. Many of those children never get to lead productive lives because they've had that critical stage of their life ruined by that single drug experience.

DRUG FREE SCHOOL PROGRAM

Mr. STOKES. The House just recently, in a rescissions package, cut the money from the safe and drug free school program. Does that have an impact on what you're talking with us about now?

Dr. LESHNER. We believe that the prevention programs in schools are very important and a very integral part of the entire panoply of prevention programs in this country. And although we haven't evaluated all of the individual programs, and I can't speak for any individual program's usefulness, I can tell you that there are many school-based programs that have been evaluated and shown to be very useful.

DRUG ABUSE AND AIDS

Mr. STOKES. Doctor, AIDS has now become the leading cause of death in people 25 to 44 years of age. What progress have we made in advancing the understanding and in unraveling the impact of drug abuse on the immune system? And, to what extent has that knowledge broadened our understanding of AIDS and immune deficiency diseases?

Dr. LESHNER. Let me say first of all that I'm sorry to have to report that drug abuse is now, according to the CDC, the largest vector of new cases of AIDS in this country. We have a large program, as a part of our overall AIDS portfolio, that is looking at the question of the influence, particularly of opiates and cannabinoids, on immune function.

I think that I would say at the moment that there's some evidence that there are receptors on immune cells, but that that's not yet definitive. There is some evidence that suggests that drugs of abuse can influence the course of development, the pathogenesis of HIV to AIDS. One of the reasons that we have such a large research program in that area is to try to determine exactly what the influence is. We recently had a major international conference on this issue. I would say that the results were hopeful in terms of informing us, but we don't have a definitive answer at this time.

PHARMACOLOGIC TREATMENTS

Mr. STOKES. Okay. According to the justifications for your Institute, the average return on every one dollar invested in treatment programs is seven dollars. As the Institute seeks to develop pharmacological treatments for drug addiction, are researchers placing enough emphasis on helping to ensure that new pharmacological treatments are not just as addictive and threatening to the quality of life?

Dr. LESHNER. Absolutely. We are very concerned about using a variety of strategies in the development of medications. We do have medications for the treatment of heroin addiction, but sadly, methadone, as you know, although an extremely effective treatment, does have addictive potential.

Although I will, if I may, remind everyone that a methadone patient who is a very successful lawyer testified before this committee a short while ago. Many, many people on methadone are able to return to a full productive life. So the phenomenon of the compound being addicting should not be confused with its effectiveness as a treatment modality.

However, we are working very hard to look at different strategies, as I implied before, based primarily on what we've now learned about the modes of action in the brain of these various drugs of abuse. We're now looking at a wide range of strategies, hopefully to develop medications in a short period of time, that won't have those addictive or abuse potentials. We're making some progress. We have some compounds that are in initial clinical trials.

Mr. STOKES. For any of the addictive drugs, are we close to having an effective treatment?

Dr. LESHNER. Well, I believe the methadone is an effective treatment, sir.

Mr. STOKES. Do you?

Dr. LESHNER. I do. I believe that it reduces criminality and, when used with a full panoply of behavioral therapies, it significantly reduces recidivism. It reduces relapse, which is the major problem, of course, that we have. It reduces re-incarceration. And of course, it reduces seroconversion rates to HIV. So it is an effective medication. However, it's nowhere near as effective as I would like it to be. And, as I said before, we don't have any medication for cocaine addiction, which is right now our highest priority.

Mr. STOKES. Is there any basis for people to feel that people become methadone addicted?

Dr. LESHNER. People do become physiologically dependent on methadone. But again, we have many patients who have been on methadone for 10 years leading perfectly normal lives. I don't believe that the fact that it is addicting is the major problem. The problem is the craving for the heroin that we're trying to treat. We do over time, through a variety of psychosocial treatments combined with methadone treatment, hope to be able to get people off totally. And there are many, many, many successes. But that is the best thing that we have available at the moment.

GENE THERAPY

Mr. STOKES. And my last question, Doctor, is as we have and continue to learn more about the biological factors associated with drug addiction, to what extent have researchers been able to apply the techniques of gene therapy to the treatment of this disease? How far are we away from having an effective treatment in this respect?

Dr. LESHNER. We have a very large portfolio, actually, using molecular genetic techniques to understand the mechanisms of drug action. And we have a large portfolio looking for the genetic factors underlying vulnerability. Of course, we believe there's a major genetic component of vulnerability to addiction. Not everyone is vulnerable to addiction, and not everyone is as easily vulnerable to addictions. We have a large portfolio in each of those areas looking at the genetic relationship. We don't yet have a target for gene therapy. And we have not done any directly.

Mr. STOKES. You've got a big job. And it's obviously a national problem. It's one that I think carries with it a sense of urgency in terms of our trying to arrive at some solutions to some of these basic problems.

I thank you very much.

Dr. LESHNER. Thank you, sir.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. BONILLA [presiding]. Thank you, Mr. Stokes.

Dr. Leshner, thank you for being with us today.

Dr. LESHNER. Thank you, sir.

[The following questions were submitted to be answered for the record:]

FUNDING ALLOCATION TO BEHAVIORAL VERSUS BIOMEDICAL RESEARCH

Mr. Porter: How much funding do you allocate to behavioral versus biomedical research?

Dr. Leshner: The nature of drug abuse and addiction requires that research projects frequently employ both behavioral and biomedical scientific approaches. Any calculation of the funding in each of these two areas therefore requires a distinction and segregation of the research that is somewhat artificial. With that in mind, the best estimate is that in 1994, $326.5 million was obligated for biomedical research, and $44.5 million was obligated for research whose core focus was behavioral science.

DRUG USE RESEARCH AMONG HISPANICS

Mr. Bonilla: Do the funds spent by NIDA on drug use research among Hispanics reflect the extent of the problem in these communities?

Dr. Leshner: Forty-six of NIDA's 1994 projects, at a cost of about $23 million, were related to Hispanic populations. In addition to over 20 R01 awards, these projects included center grants, AIDS cooperative agreement projects, and a minority institution development award. For example, NIDA prevention research centers at Cornell University, and the University of Illinois at Chicago were supported. As of September 30, 1994, Hispanics have made up 24.3 percent of the participants in NIDA's Cooperative Agreement for AIDS Community-Based Outreach Intervention Research Program ("Coop"). The Coop program targets out-of-treatment drug users in 22 cities in the U.S. and Puerto Rico for HIV counseling, antibody testing, and experimental intensive HIV interventions. Hispanics constitute 15 percent or more of the Coop participants in eight cities: Denver CO, Flagstaff AZ, Hartford CT, Houston TX, Long Beach CA, New York NY, San Juan PR, and Tucson AZ.

Two R01 grants and a minority center award illustrate the type of work being supported to clarify epidemiologic questions and to advance the etiologic base for successful interventions with Hispanic populations. Dr. William Vega has an R01 award to study patterns of drug use in Hispanic and Non-Hispanic male teens. His research has two primary objectives: 1) to conduct comparative epidemiologic assessments within and between different ethnic and racial subgroups; and, 2) to test a number of theories and theoretical assumptions regarding the initiation, progression, cessation and maintenance of drug use among a cohort of early adolescent boys. The study results are intended to provide important information about adolescent drug use as it occurs among non-Hispanic Whites, non-Hispanic Blacks, and a variety of Hispanic ethnic background students including those of Cuban, South American, and Caribbean Basin heritage. It is also intended to assess the role of acculturation processes and conflicts with the initiation and continuation of drug use among Hispanic background adolescents. Dr. Ernest Chavez is conducting a followup longitudinal investigation of the relationship between school dropouts and drug use among Mexican-American youth. Subjects are being followed into the earliest stages of young adulthood to determine how drug use interacts with psychological, social, and cultural characteristics to influence the short-term outcome of dropouts and academically at-risk youth. Dr. Jesse Zapata has support for a minority research center. The specific aims of this center are to: conduct a drug epidemiology and needs assessment study of the adult intravenous drug using population in two areas of South Texas - San Antonio and Laredo: develop a model intravenous drug use assessment approach that meets particular social and cultural characteristics and conditions of the Mexican-origin populations in the Southwest; implement and test the validity of this model over a three year period; and enhance the University of Texas at San Antonio's capabilities in the development and implementation of substance abuse research among Latino faculty and students. The model will be applicable to Southwestern urban and border communities.

Some of the other studies NIDA supports focus on the role of psycho-social factors in the progression, maintenance and cessation of drug use in Hispanic male adolescents; the effects of prenatal crack abuse on infant development; retaining drug abusing youth in family therapy; TB prevalence and treatment use among drug users in Puerto Rico; and community based HIV risk reduction at the U.S./Mexico border.

Drug abuse is a major health problem for Hispanic populations in the United States. Persons of Hispanic origin comprise about 9 percent of the total U.S. population; yet in 1989 nearly 14% of drug abuse related deaths in 27 metropolitan areas occurred among Hispanics and Hispanics accounted for more than 17.5% of Americans in drug treatment. One NIDA supported study found, however, that nearly 45% of Hispanic intravenous drug users have never been in treatment. In addition, HIV/AIDS is disproportionately represented in the Hispanic community. As you point out, Hispanics make up over 15 percent of the AIDS cases in the U.S., with drug use being their major source of infection. More than 30,000 Hispanics developed AIDS by 1991, and of that number about 46% developed the disease through intravenous drug abuse. Furthermore, three quarters of Hispanics who developed AIDS through heterosexual transmission had sexual intercourse with an IV drug user. The great majority (over 80%) of Hispanic children with AIDS were born to mothers whose risk for HIV infection was associated with their own intravenous drug abuse or sex with an intravenous drug abuser.

Recent analyses of drug use in school age populations (i.e., Monitoring the Future) revealed increased use of marijuana among 12th, 10th and 8th graders. Although sample sizes are small, preliminary analyses by ethnicity showed that Hispanic youth in comparison to white and African-American youth reported higher rates of cocaine and crack use at all grade levels. Moreover, Hispanic youth seemed to show higher use of most drugs assessed at the earlier (8th) grade level.

Mr. Bonilla: Hispanics make up over 15 percent of the AIDS cases in the U.S., most of whom contract AIDS through drug use. Are funds commensurate with the extent HIV in this population?

Dr. Leshner: As you point out, Hispanics make up over 15 percent of the AIDS cases in the U.S., with drug use being their major source of infection, and therefore we are focusing particularly on special problems and issues for the Hispanic community. For example, as of September 30, 1994, Hispanics have made up 24.3 percent of the participants in NIDA's Cooperative Agreement for AIDS Community-Based Outreach Intervention Research Program ("Coop"). The Coop program targets out-of-treatment drug users in 22 cities in the U.S. and Puerto Rico for HIV counseling, antibody testing, and experimental intensive HIV interventions. Hispanics constitute 15 percent or more of the Coop participants in eight cities: Denver CO, Flagstaff AZ, Hartford CT, Houston TX, Long Beach CA, New York NY, San Juan PR, and Tucson AZ.

In addition, other NIDA supported studies examining HIV/AIDS in Hispanic populations include a study at the Hispanic Health Council in Hartford, Connecticut on the effectiveness of needle exchange and research at the Ponce School of Medicine (Puerto Rico) that examines HTLV and AIDS in Puerto Rican IV drug users. Further, basic research being conducted on HIV/AIDS and research done in other communities can also be of benefit to Hispanic populations.

Mr. Bonilla: What percentage of current NIDA research funding goes to projects whose subjects are predominately Hispanic?

Dr. Leshner: NIDA supports 46 projects that focus on or are related to Hispanic populations or issues. (This means that these projects have research questions/issues that are Hispanic specific or include Hispanic people in sizeable numbers.) These projects account for about 7% of NIDA's extramural research dollars.

Mr. Bonilla: What programming efforts do you currently have to increase Hispanic representation in NIDA's intramural and extramural research?

Dr. Leshner: NIDA is committed to increasing Hispanic representation in our intramural and extramural research. We started an Hispanic Initiative in 1994. The purpose of this initiative is to plan efforts to broaden and ensure the appropriateness of NIDA's research program on drug abuse in Hispanic populations, and to increase the number of Hispanic scholars engaged in drug abuse research. This initiative has several components. In large part, it works under the advisement of Hispanic scholars and researchers, the Hispanic Work Group, who provide guidance and advice in the assessment of the field and make recommendations for research expansion. As a result of the initiative, a program announcement is planned, alliances with individual researchers and organizations have been formed, ideas to pursue for other collaborations are being discussed, and work group members have participated in other NIDA meetings, such as the drug abuse research training issues in minority populations held in January 1995 and Hispanic materials development planning meeting held in March 1995. In addition, the Hispanic initiative, which is based in the Office of the Director, has emphasized to NIDA program divisions the continued importance of addressing Hispanic population concerns which has led to greater efforts to include Hispanic issues in division activities, e.g., technical reviews, conferences, research studies. NIDA is aggressively engaged in a number of efforts to increase Hispanic representation in NIDA's extramural research programs. For a number of years, NIDA has systematically provided technical assistance to minority investigators on grant development issues related to drug abuse research through its Special Populations Research Seminar Series. A number of Hispanic researchers have been involved with this program and have become successful grantees. Further, some have gone on to become members of IRGs and other advisory groups.

NIDA's intramural division sponsors the MRTP (Minority Research Training Program) which provides mentored research experiences to minority students and faculty. Students work with intramural scientists during the summer in hopes that they will consider drug abuse research as a career. Hispanic students have participated in the summer program.

Mr. Bonilla: What is NIDA doing to improve research partnerships with the Hispanic communities and community based organizations?

Dr. Leshner: Through its Hispanic initiative, NIDA has been developing relationships with Hispanic organizations. The Hispanic Work Group has members who represent university and community-based organizations. Meetings are regularly held with work group members and leaders to discuss possible strategies and ways to implement them. Another meeting with the work group will be held in April 1995 to discuss recommendations the group has made regarding specific research initiatives and research training needs with an emphasis on discussing developing research involvement with community-based organizations.

NIDA has also provided support to programs designed to expose Hispanic high school and college students to science and biomedical careers. These include support to the Interamerican College of Physicians and Surgeons and a local community-based organization that provides tutoring and other programs, e.g., leadership development, to low-income Hispanic youth.

Mr. Bonilla: NIDA's Hispanic Initiative is a commendable action step towards addressing drug abuse and AIDS issues specific to American's Hispanic communities. Has NIDA made a commitment to ongoing funding for this activity?

Dr. Leshner: Yes. FY 1995 funds have been committed to continue the activities supported under the Hispanic Initiative, and funding is expected to continue next year.

Mr. Bonilla: Has there ever been any sustained efforts addressing Hispanic community substance abuse issues and needs? If so which were these and what were their outcomes and lessons?

Dr. Leshner: Efforts to address Hispanic issues have been part of the larger minority programs. These programs include NIH-wide type programs such as the MARC, MBRS and Minority supplement programs. Also a requirement that minority groups be included in study populations was established, and guidelines to ensure that representation occurred were strengthened last year. NIDA specific programs include the Special Populations Research Development Seminar Series and MIRDP (Minority Institutions Research Development Program, an ADAMHA program which is being rewritten for reissue). The Seminar Series provides mentoring to minority investigators on drug abuse research and grant development. Hispanic scholars have been involved in this activity as trainees and mentors. In addition, program divisions have released program announcements (e.g., PA 93-046 Drug Use and Abuse in Minority and Underserved Populations) or RFAs (e.g., Minority Drug Abuse Prevention Research Centers) requesting work related to minority populations and have developed informal outreach efforts to encourage research on Hispanic issues or Hispanic investigators to become active in drug abuse research. Five years ago, the Office of Science Policy, Education, and Legislation at NIDA began regular meetings with Hispanic scholars to discuss drug abuse issues in the Hispanic community. This group led, in part, to the current Hispanic initiative.

These efforts produced some positive results. They led to more research studies focusing on Hispanic populations and increased number of studies that included Hispanics in study populations. NIDA has shown yearly increases in number of grants and total dollars spent in minority related research. More Hispanic students and investigators are being exposed to the need for drug abuse research, and to opportunities for participation. These efforts also revealed the complexity of the problems of drug abuse in Hispanic populations and emphasized the need for focused, concentrated efforts on Hispanic issues. Key among these issues, for example, are acculturation and identity, language, and subgroup diversity and identity. The need for better epidemiologic data, language and culturally appropriate materials, and accessible and effective prevention and treatment became clearer. Barriers to the conduct of research and the participation of Hispanic researchers and institutions in drug abuse research are better understood. Commitment to the removal of these barriers is needed and must be conveyed to the community of scholars and organizations. NIDA has learned that it must maintain a leadership role not only in the financial support of investigator initiated research studies, but also in the development of the resources and supports needed within the Hispanic community of researchers and scholars that will encourage and stimulate outstanding drug abuse research. This is important not only to the Hispanic community, but to the entire community.

Mr. Bonilla: How many focus studies have involved predominately Hispanics?

Dr. Leshner: In FY 1994 NIDA funded 46 grants that focused on Hispanics either through the intent of the research questions or the sample representation. Finer distinctions are difficult to make within this group of 46 studies; however, at least 14 of them focused exclusively on research topics that were Hispanic specific (e.g., family function/drug use of Mexican American adolescents, to establish a national resource for drug abuse prevention research for Mexican Americans, Mexican American dropouts and drug use, HTLV I and AIDS in Puerto Rican IV drug users) or included at least one-third Hispanics in the patient/participant pool.

Mr. Bonilla: Does your agency currently have any private-public initiatives?

Dr. Leshner: NIDA has been working with the Partnership for a Drug-Free America, a private non-profit coalition of professionals from the communications industry, which has sponsored the largest mass media drug abuse prevention campaign ever undertaken. This campaign, which has earned more than $1.8 billion in broadcast time and print space, has reached millions of young people and their parents with a strong antidrug message. Since the Partnership formed in 1988, NIDA has provided the science-based information used in all of their campaigns--including information on the patterns of drug use, how drugs work in the body, the health consequences of each of the drugs of abuse, and messages derived from drug abuse prevention research. Spanish language print materials are being developed by NIDA to disseminate materials designed to educate the Hispanic audience. NIDA has also reviewed message content for accuracy.

EXTENT OF THE PROBLEM

Mr. Stokes: How extensive a problem is drug abuse in the U.S. population and how does the extent of the problem compare with that in other countries?

Dr. Leshner: Drug abuse, once termed the American Disease, is now recognized as a global issue. Countries that in the past were considered "production" or "transport" countries in which drugs were either produced (opium, coca, ganja/marijuana) or through which drugs passed to move from producing to consuming countries, are now almost universally consumers of drugs.

Problems associated with the distribution and use of drugs are fast becoming recognized by most countries in every continent and many of these countries are seeking assistance in epidemiologic methods to ascertain the extent of drug use in their countries and the characteristics of the populations using drugs.

In the United States, trends in drug use are monitored through several data systems. Two data systems assess the scope of drug using behaviors at the national level for the general population age 12 and older. The first, the National Household Survey on Drug Abuse, now under the auspices of the Substance Abuse and Mental Health Services Administration, conducts interviews among a representative sample of persons aged 12 and over residing in households and non-institutionalized group quarters throughout the United States. The second, Monitoring the Future, supported through a grant from the National Institute on Drug Abuse to the University of Michigan, gathers information from a nationally representative sample of youngsters in the 8th, 10th and 12th grades in private and public schools throughout the continental US. It also surveys individuals up to 10 years after high school. Both surveys use self-administered questionnaires.

Both of these surveys have been conducted since the mid 1970s (the 8th and 10th grade samples were added in 1991) and have shown downward trends in marijuana use since its peak period of 1978 and in cocaine use since its peak period in 1985. However, in 1992 a rise in the prevalence of marijuana was noted in Monitoring the Future Study among 8th graders, a rise that has continued. Since 1993, use of marijuana increased in all three grades.

Many other countries are beginning to develop methods for estimating the prevalence of drug using behaviors among their citizenry. However, many lack the expertise to conduct such studies. Deciding on what drugs to ask about in surveys requires knowing what drugs are used and what they are called, what their effects are, and, how they are used. Such information is usually gathered through a number of methods. Most often, indicator data or archival data are gathered and collated to gain insights into which population groups further studies are needed. Data from police arrest reports, from records from jails and prisons, from hospital and other health (including coroners' or medical examiners' offices) and social agency records and from treatment programs help guide investigators in the development of surveys.

In order to integrate data from various sources and to provide a community-based perspective, NIDA organized a network of researchers who meet biannually to present and discuss data from quantitative and qualitative sources. Since 1976 the Community Epidemiology Work Group (CEWG) has provided NIDA the basis for ongoing epidemiologic surveillance on drug abuse patterns and trends, emerging drugs of abuse and characterization of vulnerable populations.

Following the example of the United States, a number of countries, principally in Europe -- Sweden, the Netherlands, Greece, Italy and Spain, among others -- also have conducted comprehensive surveys. Most European countries, under the auspices of the Council of Europe Pompidou Group, have developed a network of researchers who collect and analyze drug abuse indicator data on a periodic basis similar to the CEWG. Both Canada and Mexico also conduct national surveys and have active programs to monitor drug abuse among youth. In addition, both countries recently have developed research networks based on the CEWG model. The CEWG model also has formed the basis for the recent establishment of epidemiologic networks in Central America and in East and West Asia. In general, however, the availability of comprehensive data from sophisticated epidemiologic information systems is lacking in most countries of the world at present.

MOLECULAR CLONING

Mr. Stokes: The opening statement states that among the most exciting and significant discoveries of the past decade was the molecular cloning of the receptor genes for virtually all drugs of abuse. Specifically, what measurable payoff are we seeing from that investment of research knowledge and know how?

Dr. Leshner: Cloning the genes for the endogenous proteins which interact with drugs of abuse is extraordinarily important because it places new tools in the hands of scientists for studying more precisely how drugs affect people to cause both their short- and long-terms effects. For example, once a gene is obtained it can be inserted into cells to create models for determining the mechanisms of tolerance and dependence. Once a gene is available, it also can be eliminated or "knocked out" in animals to study the role it might play in the behavior of an animal, or it might also be manipulated to study its function more fully. Obtaining a gene through cloning also is critical in order to understand how it is regulated within a cell. This is crucial to understanding what turns genes on and off and how they are impacted by exposure to pharmacological agents like drugs of abuse.

Developing such systems for study often takes scientists several years after a gene is first cloned, but such studies now are vigorously underway. For example, as a result of cloning, scientists have recently discovered the properties of an endogenous inhibitor of PC2, the enzyme responsible for the synthesis of bioactive enkephalins and endorphins in the brain and neural tissue. Understanding how this enzyme functions may aid in understanding the addictive properties of drugs. Discovery of this enzyme should greatly enhance our understanding of mechanisms that regulate endorphin biosynthesis. A thorough understanding of these mechanisms might one day lead to enzyme-based drugs as therapeutic agents in opiate addiction.

Another example of research which has exploited gene discovery focuses on the interaction between gene expression and stress. Stress strongly increases gene expression in a brain region known as the hypothalamus. Using a recently developed mouse model in which certain genes were manipulated, scientists have discovered that acute morphine administration prior to stress produces marked increases in expression of a certain gene compared with stress alone. In contrast, chronic morphine administration decreases expression of the gene, and inhibits stress-induced expression of the gene. In addition, expression of the gene for endogenous proenkephalin (the parent molecule for opioid peptides) increases in parallel with the gene. These data suggest that acute morphine administration makes neurons that contain proenkephalin more sensitive to stress and that chronic morphine administration desensitizes these neurons. This model is a useful tool to investigate how opiate drugs, such as morphine or heroin, may affect the genes for the brain's own opioid peptides. This could eventually lead to the development of treatments that could aid in withdrawal and relapse prevention.

Mr. Stokes: What have been the most significant achievements over the past decade?

Dr. Leshner: During the past decade, NIDA has made significant research advances ranging from basic neuroscience to clinical treatment research. The following are a few of the most significant of these accomplishments:

BASIC RESEARCH

- The cloning of the genes for each of the opiate receptors which is leading to the development of new medications to treat heroin addiction and to better manage chronic, severe pain.

- The cloning of the gene for the dopamine uptake protein, a site at which cocaine acts in the brain, which is leading to the development of a medication to treat cocaine addiction.

- Using cloning to determine the different forms of the enzyme nitric oxide synthase (important in the biosynthesis of nitric oxide) and their roles in brain and other biological functions. Nitric oxide is involved in normal brain functioning as well as in effects from drugs. Understanding it could lead to the development of pharmacologic interventions for various drug addictions.

- The cloning and characterization of the genes encoding the proteins for the dopamine receptor subtypes (D_1, D_2, D_3, D_4 and

D_5) which opens new avenues for exploring possible differences in drugs responses.

- The demonstration of the brain mechanisms involved in drug seeking behavior and addiction which is providing the scientific basis for developing treatments for cocaine addiction.
- The demonstration of the addictive nature of nicotine which has played a key role in the development of the nicotine patch as well as smoking prevention programs.
- The discovery and isolation of anandamide, a chemical produced by the brain that is similar in action to THC, the active ingredient in marijuana. This discovery may lead to the development of new therapeutic drugs that have the positive effects of some of the components of marijuana (painkilling, antihypertensive, antinausea, etc), without the adverse psychotropic effects.

CLINICAL RESEARCH

- The development of urine screening technologies and standards to detect illicit drug usage which has made possible the national drug-free workplace initiative and provided physicians and health care providers with a significant diagnostic instrument.
- The development of procedures involving clonidine and clonidine combined with naltrexone to allow for rapid and effective detoxification from opiates.
- The demonstration of the value of treating the depression suffered by many drug abusers as a means to improving treatment outcome for their addiction.
- The development and evaluation of pharmacologic treatment for newborns withdrawing from exposure to narcotics. These medical regimens have been published and are available to pediatricians and neonatologists.
- The demonstration of successful drug abuse treatment reducing criminality as well as relapse to addiction.

EPIDEMIOLOGICAL RESEARCH

- The development of epidemiological instruments and programs that have enabled us to monitor the nature and extent of drug abuse. This was accomplished in spite of the fact that in the 1970s it was widely believed that reliable and valid surveys of illicit drug use could not be conducted.

MEDICATIONS DEVELOPMENT

- The development of naltrexone, a medication designed to block the effects of narcotics such as heroin. Naltrexone is longer acting than naloxone, another narcotic antagonist which has been credited with saving the lives of thousands of people suffering from heroin overdoses.

- The FDA approval of the opiate agonist, ℓ-alpha-acetylmethadol (LAAM) as a pharmacotherapy for opiate addiction. LAAM offers significant advantages over current methadone therapy, because it only needs to be dosed every other day, and it does not require weekend (take home) medication. This was the first new drug application ever approved by the FDA specifically for addiction treatment.

PREVENTION

- The measurement of the positive impact of comprehensive research-based community drug prevention strategies that involve the media, schools, families, neighborhoods, and the workplace.

HIV/AIDS

- The development of drug abuse outreach and intervention programs that are highly effective in reducing behaviors associated with the spread of HIV/AIDS. The development of these types of programs is critical in light of recent CDC findings which show that as of June 1994, 3 in 8 AIDS cases were related to injection drug use. In fact, drug abuse is currently the fastest growing vector for the spread of HIV, not only among drug users, but also among nondrug using populations.

- The demonstration of participation in methadone treatment significantly reducing HIV seroconversion rates and decreases high-risk behaviors.

PHARMACOLOGICAL TREATMENTS

Mr. Stokes: According to the justification the average return on every $1 invested in treatment programs is $7. As the Institute seeks to develop pharmacological treatments for drug addiction, are researchers placing enough emphasis on helping to ensure that new pharmacological treatments are not just as addictive and threatening to the quality of life?

Dr. Leshner: You have raised two very important but distinct points. The first concerns medications which may by themselves produce dependence. The second concerns quality of life. Let me address each in turn.

It is a goal of our science to produce medications which are safe and efficacious and which, if at all possible, are not capable of causing tolerance or dependence. In the ideal situation we would like to be able to cure or substantially ameliorate addiction with medications which did not have any ability to produce dependence and we will continue to strive in that direction. We developed one such medication, naltrexone, which is an opiate antagonist. As such, it prevents opiates such as heroin from having effect. However, in practice, most addicts will not take naltrexone because they must first be completely detoxified from opiates, and they know they cannot get any effect from naltrexone. Therefore, many addicts will not take, or will stop taking naltrexone. The product works best with highly motivated patients who are opiate free and wish to use the product to keep from slipping back into opiate use. Interestingly, it has just recently been approved for the prevention of relapse to alcoholism as well as opiate addiction. As with any other form of medicine, not every medication is right for every patient. For many patients, methadone or LAAM works better than naltrexone.

Insofar as quality of life issues go, it is true that in the case of opiate agonist medications, methadone (and now LAAM), the patient is nearly always dependent on the treatment medication.
It should be noted that there are other forms of medicine where patients are dependent on their medications. Diabetics are dependent on insulin, manic depressives on lithium, and in a very real sense people on high blood pressure medicine, or heart medications, need these medications to control their diseases.

While methadone and LAAM produce a physical dependence (tolerance and withdrawal), there is an important distinction between this dependence and the criteria used for diagnosis of a substance dependence disorder (addiction). As described in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, patients taking methadone or LAAM do not meet the criteria for substance abuse dependence (addiction) as that definition is considered to encompass, in addition to tolerance and withdrawal, the range of drug seeking and associated criminal behaviors (attributed to the addict population) and perseveration of drug-related activities in the face of negative consequences. These include taking substances in larger amounts or for longer periods than intended, persistent desire or unsuccessful efforts to cut-down or control substance use, excessive amounts of time spent in drug-seeking behaviors, important activities reduced or given up because of substance abuse, and continued use of the substance despite knowledge that the substance exacerbates persistent or recurrent physical and/or psychological problems. To the contrary, methadone and LAAM reduce drug seeking and other behaviors, allowing patients to hold jobs, attend school, have fewer problems with the law, and have a reduced risk of morbidity and mortality associated with addiction and the infectious diseases so often linked to injection drug use--including HIV and AIDS acquired through the sharing of dirty needles.

With these treatment medications there is no use of needles and the attendant risk of HIV, tuberculosis, and hepatitis. There is no need to find a place to "shoot-up" several times a day, and nearly no chance of accidental overdose. There is an opportunity to receive medication, counseling, and rehabilitative services. Finally, methadone treatment is vastly less expensive than incarceration or residential treatment. In short, a well-run methadone program offers a far better quality of life than that of a life on the street seeking drugs.

The Institute is shifting emphasis in the types of new medications we are seeking to develop. We are completing the development of buprenorphine, a drug with less physical dependence capacity and less risk of overdose than other opiate drugs, including methadone or LAAM. We are also pursuing the discovery and evaluation of non-opiate compounds that could impact on the addictive process. Some of these medications, if used alone, could be prescribed by physicians in a variety of settings other than a narcotic maintenance treatment program. This would improve the quality of life and esteem of the patients while allowing the more needy patients to be treated in traditional maintenance clinics until they are ready to "graduate" to a less restrictive form of therapy.

Mr. Stokes: For which of the major addictive drugs, are we close to having an effective treatment? What major research opportunities are on the horizon in this area?

Dr. Leshner: As I noted in the question above, methadone and LAAM are effective treatments for the treatment of opiate (heroin and other morphine-like drugs) addiction. There are thousands of people who can testify to that fact. Additionally, naltrexone is an effective relapse prevention agent in formerly dependent, highly motivated addicts and has been approved for the prevention of relapse to alcoholism. We are currently testing other products for the treatment of opiate addiction (buprenorphine and lofexidene) which will offer advantages over methadone and LAAM for certain patients. As in all forms of medicine, we are seeking to give patients and physicians more choices and therefore more chances for success. We believe the science now exists to enable us to do even better in this regard.

A real breakthrough would be a medication which would prevent persons who are currently detoxified from their drugs of abuse from relapsing to drug taking behaviors. A vaccine which would produce antibodies which would specifically recognize and destroy certain drugs of abuse or could neutralize their effects would be a quantum leap forward.

We do not as yet have our first approved medication for the treatment of cocaine addiction. I have made this a top priority for NIDA. As we have now cloned the dopamine transporter in the brain which is thought to be the primary recognition site for cocaine, we have the ability to design and test new strategies and therapies. We have the ability to non-invasively image (PET scan) the effects of drugs in the brain, both with and without treatment drugs on board. All of this was impossible just a few years ago.

In summary, basic neuroscience research is revealing the structure and function of the brain and its neurochemical messengers. As we become more sophisticated in our knowledge of brain structure and function, we gain the ability to understand how drugs of abuse work and how to alter their effects. This will lead to more effective treatments with less side effects for a whole variety of human conditions (including addiction) which are mediated in the brain.

PREVENTION

Mr. Stokes: Under the FY 1996 budget request, how much of the Institute's budget would be invested in prevention, and how does this compare to the FY 1995 and FY 1994 funding level?

Dr. Leshner: Under the FY 1996 budget request, 14% of NIDA's budget will be used for prevention efforts. In both FY 1994, and FY 1995, the cost of NIDA's prevention efforts was also 14% of NIDA's budget.

ADOLESCENT HEALTH

Mr. Stokes: It appears that there is a definite link between adolescent health and adult health, especially with respect to diseases and disorders that resulted from behavior choices made during adolescent years. In fact, many of the health risks that we face as a nation take shape during youth -- is there specific research and outreach underway to address drug abuse in adolescents?

Dr. Leshner: The National Institute on Drug Abuse (NIDA) supports numerous research studies that focus on young people in the effort to measure the nature and extent of drug use; to identify the causes as well as the risk and resiliency factors related to drug use; to prevent drug use and related conditions such as HIV infection; and to treat drug abuse when it is present.

Because adolescents are at high risk for initiating drug use, NIDA-supported research includes a number of studies that collect data from young people on drug use and related factors. The most visible of these efforts is the Monitoring the Future (MTF) study, which is conducted by the University of Michigan under a NIDA grant. The MTF study is the Federal Government's premier means of tracking drug use as well as knowledge, attitudes, and beliefs about drugs among the nation's youth.

Given that a variety of factors are associated with vulnerability to drug abuse, NIDA-sponsored research has been testing the efficacy of multiple-component, culturally relevant and sensitive drug prevention intervention programs to reduce risk factors, drug use, and other problem behaviors among adolescents. One such program is the Adolescent Transition Program, a 12-week multiple component educational intervention for at-risk youth (11-14 year olds) and their parents. The goal of the program is to improve family management practices and child self-regulation behaviors. Findings show that program participants exhibited gains in parenting skills, less coercive parental interactions, less family conflict, and fewer aggressive behaviors among children. The researchers are analyzing the long-term impact of the program on drug use progression. Another study used outreach in a peer-helper intervention to increase runaway youths' knowledge of HIV risks.

Drug education in the schools appears to lower the risk of substance abuse for adolescents. Research on the Life Skills Training (LST) program for middle school students supports this finding.

Students who participated in the program, in comparison to a control group of students who did not receive the program, reported 24% less heavy smoking (one pack per week), 25% less problem drinking (getting drunk more than twice a month), 35% less weekly marijuana use, and 45% less daily marijuana use. Long-term follow-up on LST with children into their senior year of high school found significant prevention effects for the use of tobacco, alcohol, and marijuana use six years after the initial program.

Analysis of drug prevention research suggests that the most promising way to prevent drug use in the long run is to provide programs based on social influence theory that focus on individuals, families, peer groups, and the community.

NIDA has and continues to support a broad range of scientifically based studies aimed at eliminating drug abuse among adolescents. These efforts include studies designed to assess the efficacy of family-based therapy (e.g., Hispanic family therapy; intergenerational and extended-family therapy) that can be provided in an outpatient clinic, at school, or in the family home; parent skills training in which teenage and adult-age parents learn how to help their children (and themselves) reduce the risk of drug use and abuse; intensive inpatient and outpatient drug abuse and psychiatric treatment for seriously disturbed, conduct disordered, violence-prone adolescents; aftercare and transitional services following treatment to prevent relapse to drug use. Other studies are designed to evaluate the cost-effectiveness of providing a community-based comprehensive program for drug abusing juvenile offenders, or of establishing an intensive case management program that maintains interservice linkages and provides assessment and placement services to drug abusing delinquent youths and their families.

NEUROLOGICAL RESEARCH

Mr. Stokes: A few weeks ago, the Committee had the opportunity to hear testimony from the nation's Nobel Laureates. They indicated that neurological research was one of the most important areas that -- if enhanced offered considerable opportunity to further medical advances. To what extent does this statement apply to the research conducted by your Institute?

Dr. Leshner: Research in the area of neuroscience is critical to understanding addiction. We now know that drug addiction is a brain disease and that all drugs of abuse act on the brain to elicit changes in behavior, perception and feelings. Some of the changes in the brain may be long-term or even permanent and may be the basis for craving and relapse. Understanding how the brain works and how drugs impact on the brain's normal functioning is essential to developing effective pharmacotherapies for drug addiction. An enhancement of research in this area offers considerable opportunities for determining the neurological basis of addiction, craving, relapse, tolerance and sensitization. This in turn could lead to the rapid development of pharmacotherapies for treating all aspects of drug addiction as well as the neurotoxicities associated with drug use.

Enhancements in neuroscience research could also lead to a better understanding of the impact drugs of abuse have on unborn babies. This is critical to the development of effective interventions that can reduce the long-term health and behavioral consequences of prenatal drug exposure.

NIDA is currently fourth among the NIH Institutes in spending on neuroscience research. In FY94, NIDA spent $200 million on neuroscience research and will spend $210 million in FY95. This investment has resulted in numerous research accomplishments that have not only provided a better understanding of the neurological mechanisms of drug abuse, but have also led to a better understanding of many other medical problems (e.g. pain management, SIDS, memory loss).

Mr. Stokes: What is the extent of the Institute's investment in this particular area of research in FY 1996? How does this compare with FY 1995 and 1994 funding level?

Dr. Leshner: In FY 1996 NIDA has allocated $210,000,000 for neurological research. This compares to funding levels of $200,000,000 in FY 1995 and $180,997,000 in FY 1994.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years, explain.

Dr. Leshner: From FY 1985 to FY 1994 the number of submitted competing applications for NIDA has nearly tripled, going from 325 applications submitted in FY 1985 to 939 in FY 1994. During this time success rates have decreased, falling from 42.5% in FY 1985 to 32.9% in FY 1994. Our FY 1995 and 1996 success rates are expected to be 25.6% and 21.3% respectively.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Leshner: The average annual cost of research project grants for NIDA has increased 6.8 percent over the 10 year period. Since the implementation of the Cost Management Plan (CMP) in FY 1991, however, the average increase has dropped below 4 percent. NIDA anticipates that the average cost of all RPGs will not exceed inflationary increases, as set forth in the CMP.

In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average annual cost of research project grants, has increased over the 10 year period by 2.5 percent. This average annual cost increase drops to -1.2 percent, since FY 1991 and the implementation of the Cost Management Plan.

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Leshner: To comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NIH is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Also, on average, approximately 5 percent of grant applicants choose not to complete the portion of the grant application referring to race and gender and have been coded in the "unknown" category. There is no way to predict the race or gender composition of those applicants. Thus, the following data may not provide a true representation of NIH's support of minority and women researchers.

The following table lists success rates for minority researchers for FY 1994, including a category identified as "unknown" for those grant applicants who chose not to identify their ethnic origin and/or gender. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of minority or women researchers.

Competing Grant Success Rates for Minority Researchers
National Institute on Drug Abuse
Fiscal Year 1994

Asian	African-Amer.	Hispan.	Native Amer.	Unknown	White	Women	HBCU
32.7	16.7	21.1	0.0	40.6	31.2	28.9	20.0

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women?

Dr. Leshner: The following data identifies the average cost of competing awards to women researchers in real and constant dollars. As stated previously, questions related to race and gender are optional on NIH grant applications. As a result, the following table identifies a gender category denoted as "unknown" which represents the average cost of competing grants for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIH's support of women researchers:

Competing Grant Average Costs for Women Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
National Institute on Drug Abuse
(Dollars in thousands)

	1985		1989		1994	
	CURRENT	BRDPI	CURRENT	BRDPI	CURRENT	BRDPI
WOMEN	113.7	113.7	156.2	128.88	235.3	156.4
UNKNOWN	94.7	94.7	188.0	155.12	249.9	166.2

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to minority researchers?

Dr. Leshner: The following data identifies the average cost of competing awards to minority researchers in real and constant dollars. As stated previously, questions related to race are optional on NIH grant applications. As a result, the following table identifies a race category denoted as "unknown" which represents the average cost of competing grants for applications in which the ethnicity of the awardee is undetermined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NIDA's support of minority researchers:

Competing Grant Average Costs for Minority Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
National Institute on Drug Abuse
(Dollars in thousands)

	1985		1989		1994	
	CURRENT	BRDPI	CURRENT	BRDPI	CURRENT	BRDPI
ASIAN	83.4	83.4	266.1	219.5	247.2	164.4
BLACK	134.6	134.6	176.5	145.63	352.2	234.2
HISP	0.0	0.0	205.7	169.72	218.7	145.4
UNKNOWN	94.7	94.7	188.0	155.12	249.9	166.2
WHITE	123.7	123.7	166.6	137.46	251.3	167.1

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to African American researchers?

Dr. Leshner: As shown in the previous table, the average costs of African American researchers in constant and current dollars are as follows:

Competing Grant Average Costs for African American Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
National Institute on Drug Abuse
(Dollars in thousands)

	1985		1989		1994	
	CURRENT	BRDPI	CURRENT	BRDPI	CURRENT	BRDPI
BLACK	134.6	134.6	176.5	145.63	352.2	234.2
UNKNOWN	94.7	94.7	188.0	155.12	249.9	166.2

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to HBCUs?

Dr. Leshner: Average costs of awards to Historically Black Colleges and Universities in current and constant dollars are as follows:

Competing Grant Average Costs for HBCUs in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
National Institute on Drug Abuse
(Dollars in thousands)

	1985		1989		1994	
	CURRENT	BRDPI	CURRENT	BRDPI	CURRENT	BRDPI
HBCU	--	--	103.3	85.23	625.6	416.0

TREATMENT FOR PREGNANT WOMEN

Ms. Lowey: I am aware that NIDA has been working toward providing pharmacotherapies for women -- particularly pregnant women. Can you tell the Subcommittee about this research? You anticipate progress in this area? Where do you expect your research will lead us?

Dr. Leshner: We do anticipate progress to be made in the treatment of pregnant addicts. We expect that this progress will be made in the nearer term in improved behavioral treatments and in the longer term in pharmacological treatments. From our viewpoint, the need for treatment for pregnant addicts is quite high as they are at risk of HIV and the vertical transfer of HIV and other diseases to the fetus.

It might be useful to characterize this research by the following time periods: currently on-going research, near-term future research, and longer term research hypotheses.

Currently on-going research:

No pharmacological therapies are currently being studied that are being developed specifically or only for addicted pregnant women. Studies which are underway at this time are being done to compare behavioral treatment methods in order to identify the most effective methods of treating addicted pregnant women and are designed to determine which methods will produce the maximum retention and completion rates for treatment. Treatment plans are tailored so that the most effective methods are matched with the specific service needs of individual patients.

Near-term research:

In addition to currently on-going research, it would be helpful to develop treatment medications that would be safe for both mother and fetus. As you know, conducting trials in this special population is extremely difficult. Most manufacturers are reluctant to allow experimental use of their products in this population for obvious issues of long-term liability. This is particularly true in a population of addicts who also often use alcohol and nicotine, as both of these substances are associated with negative pregnancy outcomes.

At the current time methadone is used in the treatment of pregnant opiate addicts. LAAM, and hopefully buprenorphine (currently in Phase III trials) may also be approved for use by pregnant opiate addicts as their use becomes more generalized and clinical experience becomes available. This is commonly how nearly all new medications for any disease are developed, i.e., they are initially approved for non-pregnant adults, and their use in pregnant women comes after a considerable experience base is developed post-marketing. There are ethical issues in proposing to test investigational compounds in this special population. In order to evaluate investigational medications in pregnant women, at a minimum appropriate teratology and reproduction studies in animals, as well as a showing of efficacy in non-pregnant females would need to be demonstrated.

Longer term research hypotheses:

As medical science learns more about the structure and function of the brain and other organs, it may be possible to actually develop compounds which affect only the mother and not the fetus. There are two ways this could be accomplished:

1) It may be possible that some aspects of addiction are controlled by receptors present in the adult but not in the fetus. For example, we know that delta opioid receptors are present in adults but not in neonates. These receptors develop later. If the delta receptor were to prove important to the treatment of addiction then it would be theoretically possible to design and test compounds which interact at that site with no similar effect on the fetus.

2) It may be possible to design medications, or vectors to carry medications, which would not cross the placenta. Such medications would circulate in the mothers circulatory system but would not reach the circulatory system of the fetus.

TEENAGERS AND DRUG USE

Ms. Lowey: I understand that NIDA is supporting research on changing trends in drug use. A study of drug use among high school seniors indicates drug use is rising. In addition to the research, I understand you are also working on a public information campaign designed to educate and prevent marijuana use. What form does this campaign take? Is it aimed at teenagers? It seems to me we need to get the message across early -- before it's too late.

Dr. Leshner: NIDA is working with the Partnership for a Drug-Free America, a private non-profit coalition of professionals from the communications industry, on a Marijuana Use Prevention Campaign to reach teens and their parents with a critical message about the dangers of marijuana use. The scientific knowledge base about these dangers, which originated in NIDA's extensive marijuana research program, are being presented in a credible and impactful way through radio and television public service announcements, booklets on the facts about marijuana use, and family-oriented videotapes. All of these materials will be distributed in collaboration with the Center for Substance Abuse Prevention, SAMSHA, who will reach the community through the States and its network of prevention coalitions.

DRUG ADDICTION AS ILLNESS

Ms. Lowey: You state that one of the most difficult challenges is to change public perception of drug abuse -- to help the public understand that addiction is a disease, not just a moral lapse. Could you explain -- in terms we can all understand -- the research that leads to the conclusion that drug abuse is a disease, not a "weakness"?

Dr. Leshner: Research in the last several years has provided an understanding of how various drugs of abuse act in the brain to mediate both acute and long-term effects. It is now known that drug use can cause long-term and possibly irreversible changes in the brain. For example, we now know the precise sites at which certain drugs of abuse act in the brain, how the drugs interact with the brain's own neurochemicals, and the circuitry involved in the drugs' effects. Research has also shown that persistent use of drugs results in alterations in the neurochemistry, structure and function of the brain, including changes in receptor number and reductions in certain neurochemicals. These changes cause the brain to work differently resulting in changes in behavior and personality. It is these changes that define addiction and make it a disease. These changes also compel a drug addict to seek and use drugs. Because the brain has changed, it is necessary for the drug addict to have the drug in order to feel normal. In the absence of the drug, low levels of brain receptors or neurochemicals will cause the brain of a drug addict to function abnormally, which will be experienced as intense discomfort by the addict. Thus, while the initial use of a drug is by choice, sustained drug use causes fundamental and persistent changes in the brain, and these changes are the essence of the illness of addiction.

There is also evidence from animal research to suggest that there may be genetic factors that predispose certain individuals to engage in drug-seeking behavior. Certain strains of mice differ strikingly in their propensity to self-administer cocaine, suggesting the existence of inheritable predisposing factors in drug abuse behavior. There is considerable optimism among researchers that it will soon be possible to identify genes that predispose humans to drug addiction. The technology is now available to study the effects of drugs of abuse on gene expression and to map in detail the genes that determine drug seeking behavior.

Ms. Lowey: You state that NIDA will "expand its efforts" in educating the public on this issue. In what ways will NIDA take on this challenge?

Dr. Leshner: NIDA is meeting with members of the National Advisory Council on Drug Abuse, drug abuse communications professionals, public relations experts, representatives of special populations, and prevention and treatment practitioners, to learn more about the public's misunderstanding about the disease of addiction, and to develop a far-reaching communications strategy for changing these misperceptions. This strategy, which will likely include print and electronic media activities, public speaking engagements, work with national organizations, and innovative telecommunications efforts, will guide our communications program for the next several years.

In addition, for the past several years, NIDA has been engaged in activities designed to improve science education in our nation's schools. These activities have multi-fold impacts, including: 1) stimulating interest among children in science; 2) increasing public literacy and interest in science; 3) increasing the public understanding of the necessity and importance of animals in biomedical research; and 4) helping to prevent drug use among children by showing them the impact drug use has on the biology of their brains. These activities have demonstrated time and time again that children have an innate curiosity about their own bodies and that providing them accurate scientific information about the biological effects of drugs has a profound effect on how they view drugs of abuse.

Ms. Lowey: Dr. Leshner, are we making any scientific progress on addiction to drugs like cocaine and heroin?

Dr. Leshner: We are making progress in the field of addiction in general, and cocaine and heroin in particular.

As I mentioned in my opening statement, we have now cloned the molecular receptor for virtually every drug of abuse. With this information scientists can move on to the cellular and genetic bases of addiction and to develop therapies based on this basic science. As an analogy, you could think of these receptor sites as tumbler locks (as in a door lock or auto ignition switch), whose structures are now known to us. We must now find the neurochemical "keys" to fit these locks. We are making important progress in this search.

The process of addiction should and can be dissociated from that of physical dependence. Addiction refers to the loss of control of drug taking which leads to compulsive use of drugs. Physical dependence occurs at the point when the neural machinery is altered in response to the continued presence of the drug. The neurobiology of addiction is being elucidated. In the area of heroin and other opiate addiction, we understand the site of action (the mu opiate receptor) quite well. This has enabled scientists to develop compounds which act in different ways at that site. NIDA has developed and brought to market two medications that operate at this site (LAAM, an alternative to methadone which is dosed less often and has less euphorogenic effects, and naltrexone, which pharmacologically blocks opiates from exerting their effect at this site). We are in Phase III testing of another product, buprenorphine, which has a ceiling effect (safer against overdose) and a milder withdrawal profile and should be useful for patients who need alternatives to methadone or LAAM.
The tools of molecular and cellular biology are offering exciting insights into the actions of opioid drugs, opening the possibility for identifying new therapeutic targets at the cellular level. We now are learning for example, that different types of opioid receptors may exist on different regions of a cell, helping to explain different drug effects and opening new means for studying the long-term cellular effects induced by drugs of abuse. These studies are important for elucidating precisely how drugs affect the brain and for following the consequences of various potential therapeutic strategies. Scientists also now are exploring how these receptors behave differently toward different drugs and endogenous ligands, and the mechanisms triggered within cells which occur when a drug binds to a receptor at its surface. We are beginning to identify the regions of receptor proteins which interact with the drugs, and with messenger systems inside cells. We are learning, for example, how drugs and endogenous substances binding to several different types of receptors at a cell's surface may trigger a cascade of events within a cell which ultimately

may explain drug effects under certain environmental conditions. Understanding the "cross-talk" among signalling pathways within cells will offer new insights into the mechanisms of receptor sensitization which may underlie the broader phenomena of tolerance and dependence observed with many drugs of abuse. They also are opening new avenues for targeting and monitoring potential therapeutic interventions for opioid abuse.

Drugs like cocaine and heroin share the ability to cause euphoria, an experience that can lead to compulsive drug use. An important substrate for the euphoric effect is the mesocortical limbic system which consists of the projection regions of the ventral tegmental area in the midbrain (ie, the nucleus accumbens and the prefrontal cortex). Because this system is dopaminergic, and because the neuropharmacology of this system has, and continues to be, intensively studied, it may be possible to use this pharmacological knowledge to design strategies to reveal the mechanisms responsible for the rewarding effects of drugs such as cocaine and heroin.

An effective strategy for treating addiction should prevent both craving and relapse. Progress is being made in this direction. For example it is known that learned associations are critical in the development of craving/relapse. It is well accepted that stimuli present in the environment when the drug is taken become conditioned to the drug experience. Thus an individual who has become drug-free may go back to the environment where the drug was taken and re-experience some of the aversive aspects of the drug (or develop a desire to take the drug). Studies in laboratory animals have shown that one of the regions of the brain critical to the development of associations is the amygdala and that lesions of the basolateral amygdala will prevent certain conditioned opiate withdrawal symptoms.

The mechanisms in brain which are responsible for physical dependence can be dissociated from those underlying drug-seeking. Compulsive drug use develops before physical dependence, which depending on the drug, might not develop at all. Heroin is well-known for its abstinence syndrome; cocaine, on the other hand, has some negative effects from abstinence, but these are not severe as those from opiates. It is of interest that the nucleus accumbens is not only relevant to drug-induced euphoria, it also plays a role in the aversiveness of opiate withdrawal.

Equally importantly, we are now at the beginning stages of important research which is separating the major effects of opiate drugs into distinct systems in the brain. We are beginning to be able separate the pain-killing effects (analgesia) from the effects of tolerance. This research holds promise that an entire new generation of medicines may be developed which could treat pain without the development of tolerance and/or dependence, and could potentially treat opiate addiction without abuse liability.

In the area of cocaine, we have recently cloned the dopamine transporter site where it is believed cocaine exerts much of its action. Cocaine binds to proteins called transporters, which control nerve signals by taking certain neurotransmitters, such as dopamine, norepinephrine and serotonin back into cells after they are released. Through molecular and cellular biology, we are -- for the first time -- beginning to understand differences in how endogenous neurotransmitters as well as drugs bind to these proteins. This progress offers the promise of exploring specific potential therapeutic agents which may capitalize on these differences. Additionally, molecular biology now is providing extremely powerful tools which enable scientists to study the role in addiction of various receptors and the brain systems in which they are located. For example scientists have long tried to identify the mechanisms associated with the cellular and behavioral consequences resulting when cocaine inhibits the reuptake of dopamine into cells. Very recently, scientists have "knocked" out one form of the receptor which binds dopamine (the D_1 receptor), showing that this receptor, indeed, appears to be involved with some of the movement activities observed when cocaine is administered to animals. Such experiments offer the potential for exquisitely manipulating various aspects of the nervous system to identify how drugs exert their long- and short-term effects. As one potential treatment strategy, we have been searching for compounds which block cocaine at that site but still allow the essential neurochemical dopamine to perform at that site. We, along with researchers at Johns Hopkins University, have just recently identified some compounds which by their chemical structure would appear to block cocaine without disruption to dopamine release and re-uptake. There is still a large amount of work to be done however. We must know whether any candidate compound for development is strong enough and durable enough to endure in the brain, whether it can be administered and absorbed appropriately, whether it has acceptable toxicity, and whether it will perform as expected in human beings.

While many scientists are working to develop medications for the treatment of drug abuse, others are attempting to develop more effective behavioral techniques. One group of intramural scientists has recently shown that a contingency management approach, in which people are rewarded to each successive drug free urine, is effective in treating cocaine abusers. This study also examined the psychological characteristics of people who responded to the treatment and those who did not. An examination of the differences in the two groups may make it possible to more effectively screen patients for these types of treatment so that only those most likely to benefit are treated, while those less likely to benefit are treated in other ways.

Ms. Lowey: Dr. Leshner, during this past week, there have been a number of media stories about a cocaine blocker your researchers have developed. What is NIDA doing about medication development for addiction?

Dr. Leshner: As I said in my opening statement, development of a cocaine treatment agent is NIDA's highest priority. NIDA is actively pursuing a multi-faceted strategy in both basic and applied research to try to bring such an agent to market in the shortest possible time.

I am sure you the media reports you are referring to concern the work of Dr. Uhl at our Division of Intramural Research, and Dr. Solomon Snyder at Johns Hopkins University. As I mentioned in the answer above, Drs. Uhl and Snyder have identified an initial chemical structure which should block cocaine at this site while still permitting normal dopamine function. In order to fully test this concept, and compounds embodying this concept, we are engaged in active negotiations with a new pharmaceutical company which received $2.5 million in start-up funding from the Abell Foundation (a philanthropic foundation located in Baltimore) specifically to try to bring a cocaine medication to market. The company will be able to co-design with NIDA, and synthesize for NIDA, many new compounds of this type in order to address the many questions described above. As you probably know, the development of cocaine pharmacotherapies is highly risk aversive for most pharmaceutical companies. Therefore, we are delighted to have a firm interested, and willing to share resources, in attempting to develop a therapeutic agent from this earliest stage.

In addition to this effort, you should also know that NIDA's Medications Development Division is actively testing compounds (currently marketed for other indications but for which there is reason to believe that they may utility in the treatment of cocaine addiction) in Phase II clinical trials. Because these compounds have already been in man, they can go rapidly into Phase II clinical testing for cocaine treatment. If a robust result is obtained in one of these trials, this will be the shortest and most direct path to a new treatment agent because nearly all of the preclinical and early clinical testing will have already occurred. Phase III testing, and expedited review by the FDA would follow in short order. In addition to clinical testing, the Medications Development Division has the capability to perform applied research in the screening, pharmacology, and toxicology testing necessary to bring a compound to the point of clinical trials.

Thus, NIDA has both a basic and applied research capability dedicated to the development of a cocaine treatment agent. This capability has been reviewed by a variety of sources, including the Institute of Medicine, and found to be conceptually sound.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

FY 1996 Budget — Page No.

Organization chart........ 36

Appropriation language........ 37

Amounts available for obligation........ 39

Budget mechanism table........ 40

Summary of changes........ 42

Budget authority by object........ 44

Administrative costs........ 46

Significant items in House and Senate Appropriations Committee Reports........ 47

Authorizing legislation........ 49

Appropriation history........ 50

Budget authority by activity........ 51

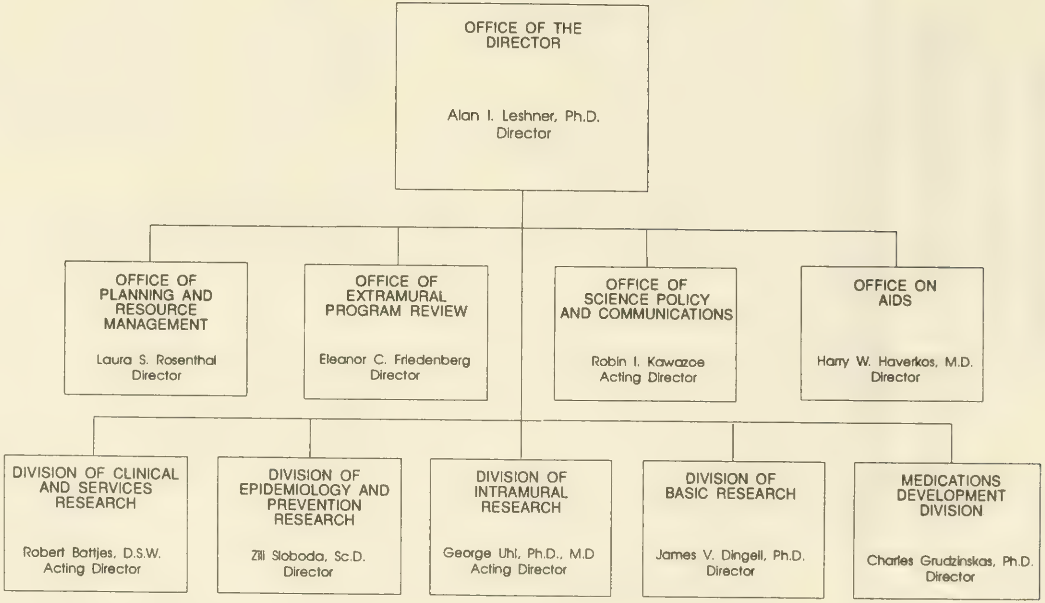
Justification:

A. General statement........ 53
B. Extramural research........ 56
C. Intramural research........ 64
D. Research management and support........ 67
E. Detail of full-time equivalent employment (FTE)........ 68
F. Detail of end-of-year employment........ 69

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Organization Structure


OFFICE OF THE DIRECTOR
Alan I. Leshner, Ph.D.
Director
OFFICE OF PLANNING AND RESOURCE MANAGEMENT
Laura S. Rosenthal
Director
OFFICE OF EXTRAMURAL PROGRAM REVIEW
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DIVISION OF CLINICAL AND SERVICES RESEARCH
Robert Battjes, D.S.W.
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DIVISION OF INTRAMURAL RESEARCH
George Uhl, Ph.D., M.D
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DIVISION OF BASIC RESEARCH
James V. Dingell, Ph.D.
Director
MEDICATIONS DEVELOPMENT DIVISION
Charles Grudzinskas, Ph.D.
Director

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National Institute on Drug Abuse

For carrying out section 301 and title IV of the Public Health Service Act with respect to drug abuse, ($290,280,000) $298,738,000.

(Department of Labor,, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

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National Institute on Drug Abuse

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$425,201,000	$290,280,000	$298,738,000
Section 513 S&E reduction.......		- 39,000	
Subtotal, Adjusted Appropriation..............	425,201,000	290,241,000	298,738,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities......	-143,376,000		
Comparative transfer to: OD, NIH for Accounting Services..................	-200,000	-200,000	
Subtotal, adjusted budget authority...........	281,625,000	290,041,000	298,738,000
Unobligated balance, ... lapsing	-707,000		
Total obligations..........	280,918,000	290,041,000	298,738,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1994 -- $3,328,000 ; 1995 -- $4,300,000 and 1 FTE; 1996 -- $4,300,000 and 1 FTE.

Also excludes funding for HIV activities: FY 1995 -- $147,402,000; FY 1996 -- $153,331,000, included in the Office of AIDS Research, NIH.

Note: Excludes $15,000 in FY 1994 and $15,000 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting..............	436	$123,606,000	472	$122,466,000	496	$132,033,000
Admin. supplementals......	(18)	598,000	(12)	446,000	(12)	464,000
Competing						
Renewal..................	76	16,228,000	88	21,563,000	83	19,368,000
New......................	134	28,463,000	94	23,030,000	90	21,321,000
Subtotal, competing....	210	44,691,000	182	44,593,000	173	40,689,000
Subtotal, res projects.	646	168,895,000	654	167,505,000	669	173,186,000
SBIR/STTR.................	33	4,858,000	21	5,069,000	26	6,507,000
Total, res projects....	679	173,753,000	675	172,574,000	695	179,693,000
Research centers						
Specialized/comprehensive.	20	21,812,000	23	25,292,000	23	25,292,000
Other research						
Research career program...	90	8,147,000	80	7,808,000	80	8,035,000
Cooperative clinical res..	2	2,082,000	2	1,375,000	2	1,414,000
Other research related....	31	3,528,000	19	1,947,000	19	2,003,000
Subtotal, other res....	123	13,757,000	101	11,130,000	101	11,452,000
Total, research grants.......	822	209,322,000	799	208,996,000	819	216,437,000

Training:						
Individual awards						
Noncompeting..............	74	1,369,000	75	1,567,000	75	1,630,000
Competing.................	0	0	0	0	0	0
Subtotal, individual.....	74	1,369,000	75	1,567,000	75	1,630,000
Institutional awards						
Noncompeting..............	160	4,053,000	164	4,592,000	164	4,756,000
Competing.................	45	1,342,000	52	1,485,000	52	1,574,000
Subtotal, institutional..	205	5,395,000	216	6,077,000	216	6,330,000
Total, training..........	279	6,764,000	291	7,644,000	291	7,960,000
Research and development contracts......	64	22,565,000	53	29,450,000	53	29,104,000
Intramural research..........	125	18,650,000	106	19,230,000	104	19,805,000
Res management and support...	261	24,324,000	280	24,721,000	278	25,432,000
Total.....................	386	281,625,000	386	290,041,000	382	298,738,000
(Clinical Trials)		(31,269,000)		(32,200,000)		(33,400,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTE OF HEALTH

National Institute on Drug Abuse

Summary of Changes

1995	Estimated budget authority	$290,041,000
1996	Estimated budget authority	298,738,000
	Net change	+8,697,000

Changes:	1995 Current Estimate Base FTE	1995 Current Estimate Base Budget Authority	Change from Base FTE	Change from Base Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$7,417,000		+100,000
b. Annualization of January 1994 locality pay		7,417,000		+32,000
c. One more day of pay		7,417,000		+29,000
d. January 1995 pay increase		7,417,000		+129,000
e. Centrally furnished svcs		51,000		+5,000
f. Service and supply fund increase		5,869,000		+183,000
g. Increased cost of laboratory supplies, materials and other expenses		11,762,000		+156,000
Subtotal				+634,000
2. Research Management & Support				
a. Within grade increase		$14,395,000		+217,000
b. Annualization of January 1995 locality pay		14,395,000		+60,000
c. One more day of pay		14,395,000		+55,000
d. January 1996 pay increase		14,395,000		+248,000
e. Centrally furnished svcs		330,000		+40,000
f. DHHS Working Capital Fund		331,000		-44,000
g. Service and supply fund increase		5,943,000		+109,000
h. Increased cost of laboratory supplies, materials and other expenses		9,665,000		+190,000
Subtotal				+875,000
Total Built-in				+1,509,000

Summary of Changes -- con't

	1995 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
B. Program:	No.	Amount	No.	Amount
1. Research projects grants				
a. Noncompeting	472	122,912,000	24	+9,585,000
b. Competing	182	44,593,000	-9	-3,904,000
c. SBIRs	21	5,069,000	5	+1,438,000
Subtotal	675	172,574,000	20	+7,119,000
2. Research Centers	23	25,292,000	0	---
3. Other Research	101	11,130,000	0	+322,000
Total, research grants	799	208,996,000	20	+7,441,000
4. Training	291	7,644,000	0	+316,000
5. Contracts	53	29,450,000	0	-346,000
	FTE		FTE	
6. Intramural research	106	19,230,000	-2	-59,000
7. Research management & support	280	24,721,000	-2	-164,000
Subtotal				+7,188,000
Total Changes				+8,697,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment...	386	382	-4
Full-time equivalent of overtime and holiday hours......	2	2	---
Average ES salary..................	$113,500	$114,600	$+1,100
Average GM/GS grade.................	10.9	10.7	-0.2
Average GM/GS salary................	$48,600	$50,000	+1,400
Average salary, grades est by act of July 1, 1944 (42 USC 207).........	$55,300	$56,000	+700
Average salary of ungraded positions	$111,800	$113,100	+1,300
Personnel compensation:			
Full-time permanent...............	$14,000,000	$14,351,000	$+351,000
Other than full-time permanent....	2,100,000	2,164,000	+64,000
Other personnel compensation......	460,000	474,000	+14,000
Special personnel services........	1,175,000	1,210,000	+35,000
Subtotal, personnel compensation.	17,735,000	18,199,000	+464,000
Personnel benefits..................	3,867,000	3,980,000	+113,000
Benefits for former personnel.......	210,000	0	-210,000
Travel and transportation of persons	495,000	510,000	+15,000
Transportation of things...........	58,000	60,000	+2,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Communications, Utilities and miscellaneous charges	2,709,000	2,750,000	+41,000
Printing and reproduction	793,000	807,000	+14,000
Other Services:			
Consultant Services	700,000	700,000	0
Other Services	7,786,000	8,333,000	+547,000
Purchases from Govt. Accounts	8,215,000	8,332,000	+117,000
R&D Contracts	26,850,000	26,504,000	-346,000
Supplies and materials	1,993,000	2,056,000	+63,000
Equipment	1,990,000	2,110,000	+120,000
Grants, subsidies and contributions	216,640,000	224,397,000	+7,757,000
Total Budget Authority by Object	290,041,000	298,738,000	+8,697,000

Note: Includes FTEs associated with HIV research activities. Funds to support these activities are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	$14,000,000	$14,351,000	$+351,000
Other than Full-time Permanent (11.3)	2,100,000	2,164,000	+64,000
Other Personnel Compensation (11.5)	460,000	474,000	+14,000
Special Personnel Serv. Payments (11.8)	1,175,000	1,210,000	+35,000
Total Personnel Compensation (11.9)	17,735,000	18,199,000	+464,000
Civilian Personnel Benefits (12.1)	3,867,000	3,980,000	+113,000
Benefits to Former Personnel (13.0)	210,000	0	-210,000
Travel (21.0)	495,000	510,000	+15,000
Transportation of Things (22.0)	58,000	60,000	+2,000
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	2,709,000	2,750,000	+41,000
Printing and Reproduction (24.0)	793,000	807,000	+14,000
Consulting Services (25.1)	0	0	0
Other Services (25.2)	7,786,000	8,333,000	+547,000
Purchases from Government accounts (25.3)	4,563,000	4,680,000	+117,000
Supplies and Materials (26.0)	1,993,000	2,056,000	+63,000
TOTAL	40,209,000	41,375,000	+1,166,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1995 House Report	
Drug Abuse Among Women	
1. The House in its report 103-553, page 62, stated: "... the Committee recognizes that HIV infection is increasing faster among women than men and that this increase is largely related to intravenous drug use. The Committee encourages NIDA to seek new pharmacologic treatments for female substance abusers, including testing drugs which may be useful in pregnant opioid or cocaine dependent women."	1. NIDA is continuing to support major efforts to develop new pharmacotherapies for the treatment of drug addiction. Within this effort is a focus on addressing the growing numbers of women drug abusers and their offspring infected with HIV. This is especially critical given the fact that over half of pediatric AIDS cases are drug-related. NIDA is encouraging studies with either marketed drugs or drugs in Phase III that look as if they will be marketed. Currently, two medications, LAAM and buprenorphine fit that category. Studies are underway which will determine if these drugs are effective in women. Additional research will characterize any potential fetal risk (as shown in preclinical teratology studies) before tests begin in pregnant women.
1995 Senate Report	
Research Training	
1. The Senate in its report 103-318, page 102, stated: "The Committee is concerned that the shortage of well-trained scientists is	1. NIDA will increase their support for training by 11% in FY 1995. In addition NIDA will set-aside additional $1.7 million for its

Item	Action Taken or To Be Taken
impeding progress in all facets of drug abuse research, and encourages additional efforts to recruit scientists with an emphasis on physician-researchers."	career development program. This will increase the number of clinicians involved in drug research.
Drug Use in Rural Areas	
2. The Senate in its report 103-318, page 102, stated: "The Committee directs that NIDA report on its research program in this area at hearings on the fiscal year 1996 request."	2. NIDA supports a significant program of research on drug use and abuse in rural communities. Over the past six years, NIDA has supported 17 individual studies for a total expenditure of $24.3 million. A report describing this program will be transmitted to the Committee.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation	Section 301	42 Sec 241	Indefinite		Indefinite	
National Institute on Drug Abuse..............	Title IV, Part C	42 Sec 285	Such sums as necessary	>$282,397,000	Indefinite	> 290,778,000
Medication Development....	Section 464P	42 Sec 285o-4			Indefinite	
National Research Service Awards..........	Section 487(D)	42 Sec 288(d)	Such sums as necessary	7,644,000	Such sums as necessary	7,960,000
Total Budget Authority..				290,041,000		298,738,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	N/A	N/A	$410,502,000	$403,806,000 2/
1994	$407,098,000	$425,201,000	425,201,000	425,201,000
1995 3/	291,963,000	290,280,000	290,280,000	290,241,000 4/
1996 3/	298,738,000			

N/A = Not Applicable.

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions. Prior to the FY 1993 Senate Allowance, NIDA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $3,272,000, $430,000, and $1,474,000.

3/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

4/ Excludes enacted administrative reduction of $39,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Drug abuse and addiction.	---	$231,275	---	$233,962	---	$238,064	---	$246,090	---	$253,501	---	+$7,411
Intramural research........	126	18,685	137	18,638	125	18,650	106	19,230	104	19,805	-2	+575
Research management and support.............	292	23,871	287	24,442	261	24,204	280	24,721	278	25,432	-2	+711
Subtotal, obligations....	418	273,831	424	277,042	386	280,918	386	290,041	382	298,738	-4	+8,697
Unobligated balance lapsing.................	---	+51	---	+94	---	+707	---	---	---	---	---	---
Total, budget authority....	418	273,882	424	277,136	386	281,625	386	290,041	382	298,738	-4	+8,697

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Justification

National Institute on Drug Abuse

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
386	$281,625,000	386	$290,041,000	382	$298,738,000	- 4	+$8,697,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute on Drug Abuse. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Drug Abuse (NIDA) is the lead Federal agency and predominant source of funding in the United States for research on drug abuse, dependence, and addiction. As a result of twenty years of drug abuse research, a tremendous amount of knowledge has been accumulated, providing a database for rational prevention, treatment, and policy making in the area of drug abuse. Through the intramural research program at the Addiction Research Center in Baltimore, Maryland and through research grants and contracts at research institutions across the country, NIDA seeks to explore the scientific bases for the development of effective biomedical, behavioral, and psychosocial approaches to the prevention and treatment of drug abuse, and for supporting research on the relationship between drug use and AIDS, tuberculosis, and other medical problems. In addition, NIDA supports research training and career development, as well as science education activities. NIDA funds almost 90% of research on drug abuse in this country. Since relatively little drug abuse research is conducted elsewhere in the world, most of what is known about drug abuse and addiction has been derived from NIDA funded research. A total of four percent of the Federal budget for drug abuse control is spent on research and development, which includes NIDA research.

The cost of drug abuse to the nation is multi-dimensional, causing harm to health, family life, the economy and public safety. In economic terms, drug abuse cost this country a total of $67 billion annually according to a study by D.P. Rice. Drug-related hospital emergency room episodes have continued an upward trend begun in 1991, and in the first half of 1993 were up 9% from the same period in 1992. Of critical importance, drug-related behaviors, such as needle sharing or having sex with an injection drug user, are the second leading cause of AIDS, and complications of drug abuse include other health effects such as cardiovascular and pulmonary disorders, tuberculosis, and other infectious diseases. Many cases of child abuse and neglect are attributed to illicit drug use among parents. Children of drug abusing parents constitute one of the highest risk groups for later-life substance abuse and other behavioral and psychosocial problems. Drug related crime that is paralyzing our cities contributes to the high cost of law enforcement and criminal justice. Almost one-third of those convicted of burglary committed their crimes to obtain money to purchase drugs, and in FY 1992, law enforcement agencies reported nearly one million arrests for drug abuse violations. American society pays the bill for the health, social, and law enforcement costs of drug abuse.

Treatment for drug abuse can occur in a variety of settings, and can significantly reduce drug use, and importantly, related criminal behavior. Consequently, the benefits of drug abuse treatment to society far outweigh the costs. A recent study conducted for the Health and Welfare Agency in California found that treatment for drug abuse resulted in substantial cost savings to taxpayers, with a $7 return for every dollar invested in treatment. Investigators found that an expenditure of $200 million in treatment costs resulted in $1.5 billion in savings by the first year after treatment. Improvements were found both in health care, and in criminal activity, which accounted for the largest proportion of the savings. Further, the costs for treatment are far below the costs of likely alternatives. For example, one year of methadone treatment or outpatient treatment costs approximately $3,500 compared to the estimated $43,000 one year of untreated addiction costs society. The cost of a year of residential treatment is approximately half the nearly $40,000 cost of incarceration. In spite of these advances and potential cost savings, drug abuse treatments are far less effective than they need to be. Thus future drug abuse research leading to needed improvements in prevention and treatment will lead to even further economic benefits.

The President's appropriation request of $298,738,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute on Drug Abuse non-AIDS activities during the last five years has been as follows:

	Amount	FTEs
FY 1991	$260,968,000	375
FY 1992	273,882,000	418
FY 1993	277,136,000	424
FY 1994	281,625,000	386
FY 1995	290,041,000	386

Purpose and Method of Operation

NIDA's research programs support basic, clinical, and applied research studies of drug abuse and addiction and related conditions. In addition, NIDA supports research training and career development, science and public education, and research dissemination.

Drug abuse research is a diverse area of scientific inquiry, with activities ranging from basic studies of molecular mechanisms to applied studies of drug abuse treatments. Taken together, this research represents the efforts of hundreds of scientists working together across multiple disciplines of psychology, psychiatry, pharmacology, biochemistry, epidemiology, clinical medicine, behavioral medicine, and the neurosciences, at universities, medical centers, and at community clinics.

Overall Budget Policy

The FY 1996 budget request for NIDA is $298,738,000, an increase of $8,697,000, or 3.0% over the comparable FY 1995 level of $290,041,000. The request provides support for 496 noncompeting research project grants, 173 competing grants, and 26 SBIR grants for a total of 695 projects.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, grant awards are limited to a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs. Competing research project grants are limited to the Biomedical Research and Development Price Index (BRDPI) increase of 4.2%.

The FY 1996 budget request will support 23 research centers at $25,292,000, the same dollar level as FY 1995.

The request includes $8,035,000 for research career programs, an amount sufficient to maintain the program at the FY 1995 level. The number of career awards are estimated at 80 for both FY 1995 and FY 1996. The request includes $1,414,000 for clinical cooperative research grants. The request includes $2,003,000 for other research related grants. Included in this category are the small grants program, science education grants, minority institution support, and instrumentation grants. In FY 1996 53 research contracts will be supported at $29,104,000, as compared to 53 contracts for $29,450,000 in FY 1995.

The FY 1996 research training request would support 291 full-time training positions at $7,960,000, the same number of training positions as in the FY 1995 appropriation and a funding increase of 4.1% or $316,000.

The FY 1996 request includes $19,805,000 for intramural research, an increase of $575,000 over the FY 1995 comparable level of $19,230,000. For research management and support, the FY 1996 budget request is $25,432,000, an increase of $711,000 over the FY 1995 comparable level of $24,721,000. This provides an increase of 3% for intramural and 2.9% for research management and support.

National Institute on Drug Abuse

Extramural Research

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$238,651,000	$246,090,000	$253,501,000	+$7,411,000

The drug abuse and addiction activity represents the extramural research and research training programs of NIDA. Funding for Extramural Research during the last five years has been as follows:

	Amount
FY 1991	$221,028,000
FY 1992	231,324,000
FY 1993	233,962,000
FY 1994	238,651,000
FY 1995	246,090,000

Rationale for the Budget Request

With the FY 1996 extramural request these funds will provide support for the following activity: drug abuse and addiction, $253,501,000, an increase of $7,411,000 or 3% over the FY 1995 appropriation of $246,090,000.

Neurobiology of Drug Abuse and Addiction

Two decades of advances in the neurosciences have provided astonishing insights into the brain and its interactions with drugs of abuse. Many questions are now being answered about the biology of the brain, how drugs affect the brain, and why drugs alter behavior. Recent developments in imaging technology allow researchers to actually visualize the effects of drugs on the brain as they are occurring. Advances in neuroscience research provide clues to help understand why drug-induced euphoria occurs, what role environmental variables, learning and memory play in the addiction process, what biological and behavioral mechanisms are occurring in the interrelated phenomena of craving, addiction, tolerance and dependence, and finally, what can be done to break the addiction cycle. Receptors in the brain have been identified and genetically specified for every known major drug of abuse, providing the base for even greater advances in understanding and, importantly, a base for strategic treatment development targeted at brain sites of action.

The cloning of genes associated with fundamental biological processes and pathological states has resulted from progress in the field of molecular biology. Addiction scientists have had an important role in this progress. The application of cloning technologies moreover can expedite the discovery of gene variants that may make individuals vulnerable to addiction, and facilitate the development of cellular models to study the molecular basis for tolerance and dependence. This information is critically important because it opens the way for targeting the development of interventions that can block the addictive properties of drugs, or can inhibit or prevent their harmful sequelae on the brain's functioning.

In order to more aggressively exploit the advances in the neurobiology of addiction, NIDA plans to pursue a major human neuroscience research program that will focus on the mechanisms of addiction and the development of new therapeutic interventions for the drug abuser. Using noninvasive brain imaging techniques, such as are available with the PET technologies, will provide data that will allow researchers to tailor individual treatments based on individual neurochemical and metabolic abnormalities.

Several models have now been developed to explain fundamental behavioral and biological mechanisms of addiction. Research will be initiated that will use current, or develop new, noninvasive techniques to assess neuroanatomical, neurochemical, or other functional differences or changes in human brain that contribute to vulnerability to drug abuse and addiction. The objective of this research initiative is to translate the research information into novel prevention, diagnostic, and treatment strategies.

As a parallel effort, NIDA is also an active participant in the Human Brain Project, a multi-agency collaboration in which an extensive computer network and database of neuroscience information is being developed. Models of the structures, functions, and molecular biology of human and animal brains reflecting normal and diseased states will increase the ability of neuroscientists to understand the biology of drug abuse, and provide a more informed basis for its effective treatment and prevention.

Already in the clinical neuroscience field, imaging techniques have enabled visualization of the human brain in both normal and drugged states, and brain activity in the presence of drug-related stimuli but the absence of drug. At the cellular and subcellular levels, discoveries are leading to the description of mechanisms responsible for long-term changes in the central nervous system associated with addiction, including gene regulation. The further exploration and application of findings from such multidisciplinary approaches will form the bases for systematic efforts to characterize the neurobiology of addiction across the spectrum from drug use to addiction, and from craving to relapse.

Treatment Improvement and Health Services Research

Using basic research findings as a foundation, new strategies for the effective treatment of drug abuse and addiction can be developed, using both pharmacological and behavioral approaches. The combination of pharmacological medications with behavioral approaches, tailored specifically for different patient subgroups and different drugs of abuse will match patients with treatment modalities to improve treatment outcomes. Drug abuse treatment research is represented by two major, interrelated components at NIDA: the Medications Development Program and the Behavioral and Psychosocial Treatment Program, with an overarching emphasis provided by the Health Services Research Program, which looks at treatment programs in real-life settings.

Health services research is a critical component because of its ability to answer questions about the cost-effectiveness of drug abuse treatment services; the effects of public and private financing and coverage on drug abuse treatment outcomes, service delivery and utilization; and approaches for altering the practices of drug abuse practitioners and other health care providers. NIDA supports a significant portfolio of research on the organization, financing, and management of health services and their impact on the quality, cost, and outcomes of care both within established service delivery settings and at a system-wide level. In addition, research in this area seeks to understand the relationship between drug abuse treatment and the delivery of services within other organized systems, such as social welfare, criminal justice, mental health, primary health care systems. Studies on the factors that influence the availability, accessibility, and utilization of health services, and the efficiency and effectiveness of these services are also ongoing.

Future research initiatives seek to determine the short- and long-term results of resource utilization controls and cost management strategies in terms of access to and utilization of services, health and social costs, outcomes and cost-effectiveness. Linkage of drug abuse treatment to primary care, refined service delivery models for outreach to populations at risk for HIV infection, and improved quality of and access to prevention services are also objectives of health services research.

Behavioral and Psychosocial Treatment. Although pharmacotherapy has proved a successful adjunct in treating addiction to some drugs of abuse, behavioral therapies are the most frequently used treatment for drug addiction, and in the case of some drugs, currently are the only available treatment. Behavioral therapies encompass a range of psychosocial interventions, including individual and group psychotherapy, psychodynamic and interpersonal psychotherapy, behavior therapy, cognitive psychotherapy, family therapy, drug abuse counseling, vocational rehabilitation, skills training, and relapse prevention strategies.

Drug abuse treatment is best seen as the management of a chronic, relapsing disease. As such, a treatment goal of complete and permanent abstinence is not always a reasonable expectation, just as complete symptom elimination is not currently possible with other chronic diseases like hypertension, diabetes, and asthma. Further, because drug addiction is often compounded by one or several other conditions, effective treatment of drug addiction requires a comprehensive approach to dealing with a patient's multiple problems. To increase engagement, retention and compliance of patients in treatment, interpersonal and environmental factors, as well as coexisting psychiatric and medical problems need to be considered. Providing an optimal combination of services for each client is critical to successful treatment outcome.

Of existing forms of behavioral therapy, most were neither designed nor tested for drug abuse populations. Consequently, NIDA has initiated the Behavioral Therapies Development Program, which is comprised of four components. Phase I involves identifying promising research findings relevant to drug abuse treatment, generating and formulating new psychobehavioral therapies, operationally defining them, and pilot testing and modifying the therapies. Phase II consists of small-scale efficacy testing of promising therapies and the replication, at other sites, of efficacy studies with positive results. These first two stages are ongoing. Once therapies are found to be efficacious in more than one controlled clinical trial, using multi-site studies to determine their effectiveness in community-based treatment programs, Phase III will commence, in which efficacious therapies will be tested. Finally, in Phase IV, panels of experts will be convened to evaluate the results, and where substantial evidence for effectiveness is demonstrated, will seek to present the therapeutic options in a way that can be applied most effectively by practitioners.

Recent findings from multidisciplinary teams are providing an informed basis for the strategic, rational development of behavioral therapies. For example, NIDA researchers have begun to separate the behavioral phenomena of craving from drug seeking. These data can help us to understand the mechanism of craving and how it relates or does not relate to drug seeking behavior. This is significant in that it refutes the long-held belief that drug seeking is only a response to craving, and opens the way for targeted treatment interventions. Moreover, recent evidence from the NIDA intramural research program has shown that identifiably different personality types respond differently to incentive-based treatment approaches. For example, people with antisocial personality disorders respond to this type of treatment differently than individuals who do not display these traits. Findings such as these are important because of the foundation they provide for the effective matching of treatment modalities to subtypes of patients.

Medications Development. Research leading to the identification, synthesis, development, and approval of new medications to reduce drug abuse and addiction is supported by NIDA's Medications Development Program. Normally, steps completing the processes from drug development through approval and utilization take 8-10 years. With a firm commitment to accelerate this process as one of its goals, NIDA established its Medication Development Program in FY 1990, and has already been successful in bringing forward a medication, levo-alpha-acetylmethadol (LAAM), for the treatment of heroin addiction. Progress has also been made in developing, testing, and gaining approval for other medications to treat drug abusers. For example, a clinical trial of buprenorphine for the treatment of opiate dependence was recently completed by NIDA, with results showing an impressive safety record for buprenorphine and the advantage of a more moderate withdrawal profile than for methadone. An injectable/implantable depot system currently in development will provide drug effects over a period of one month after a single dose. Early results testing a subcutaneous depot injection of the opiate antagonist naltrexone, show effectiveness in blocking an intravenous dose of morphine for one month, and no serious adverse effects. Use of depot systems with once-a-month dosing could greatly improve compliance and eliminate diversion associated with take-home medications.

The techniques of neuroscience have been used to investigate the effects of various mechanisms for inhibiting or interfering with the addictive properties of drugs of abuse. Cocaine and crack cocaine abuse, which has been resistant to treatment with pharmacotherapeutic agents, presents a unique challenge in medication development. The recent cloning of the gene for the dopamine transporter, a brain site at which cocaine is believed to act, revealed the structure of this transporter and rapidly led to important insights on how cocaine works in the brain. Using this information as a basis, the Cocaine Treatment Discovery Program seeks to synthesize and screen novel medications that can block the action of cocaine by various mechanisms. If a variety of medications for the treatment of addiction are successfully developed, physicians could prescribe medications aimed at specific patients at specific points in their rehabilitation. For example, a medication that blocks the euphoria produced by crack/cocaine would be useful for the primary prevention of those at high risk for crack/cocaine abuse, while another medication could help prevent those who have been successfully treated from suffering relapse.

Future NIDA research will build on these exciting developments in neuroscience. Priority will be set on developing cocaine treatment medications, with a specific longer range objective of developing cocaine medications for pregnant women that will not harm the fetus.

Fetal and Child Development

Fetal health and development are known to be adversely affected by maternal drug use during pregnancy, and the issue of paternal drug abuse prior to and during conception is being recognized as a potentially important problem. Once born, infants and children living in an environment of parental drug abuse are more likely to suffer from the negative affects of violence, dysfunctional parenting, and excessive use of alcohol and tobacco in the family. In addition, and of critical importance, the majority of reported pediatric AIDS cases are among children born to mothers who have been injecting drugs or who have had sexual contact with an injecting drug user. NIDA continues to aggressively pursue a program of research in fetal and child development as they are affected by substance abusing parents.

Although some negative effects of drug abuse during pregnancy are seen in offspring immediately after birth, others have a delayed onset and may only be visible after some months or years. For example, while a drug-exposed newborn may exhibit few or no symptoms at birth, serious learning problems might be detected in elementary school or later. Negative effects can be variable in duration, and some effects are transient, disappearing for some time only to reappear at a later stage. Therefore, it is necessary that the effects of prenatal drug exposure are assessed repeatedly during development as well as during infancy.

Ongoing NIDA-supported studies are in the process of examining consequences of prenatal drug exposure in the first three years of life. In order to follow children beyond three years of age, participation with the National Institute of Child Health and Human Development, the Center for Substance Abuse Treatment, and the Administration for Children Youth and Families, in the multi-site Maternal Lifestyle During Pregnancy and Neurodevelopmental Outcome Study will be extended, and competitive renewals will be funded for high-quality individual cohort studies. Data from these studies will document drug-exposure, developmental progress from birth onward, environmental variables through the first years of life, and consequences of prenatal drug exposure, and thus will form the basis for developing preventive interventions for this population. Other NIDA studies are looking at the effects on the neuroendocrine, cardiovascular, and respiratory system of the developing fetus caused by maternal drug use.

Fetal and child development research areas that will be explored by NIDA in the future include the development of effective intervention/prevention procedures for women and their children within a family context, the identification of parental or other factors that compound or reduce the effects of drug exposure, and longitudinal research to determine the developmental effects that result from drug exposure that occurs preconceptually or postnatally.

Epidemiology and Prevention

NIDA supports epidemiologic studies to explore the origins and causes of drug abuse among individuals, as well as the patterns of drug abuse in specific populations. Prevention research is supported so that promising ways to prevent initial drug use can be identified, the progression from drug use to abuse interrupted, and the likelihood of relapse reduced.

Although drug use has been on a continuing downward trend since 1979, the numbers of heaviest users has remained relatively constant. However, more alarming are the findings that drug use and attitudes about drugs among our young people are worsening. NIDA supports the Monitoring the Future Study, which includes data on drug use and related attitudes among eighth, tenth, and twelfth graders. The survey, first known as the High School Senior Survey, has been conducted each year since 1975. Findings released in December 1994 confirm the increase in marijuana use first seen last year among tenth and twelfth graders and in 1992 among eighth graders. Survey data also point to the gradual rise in the use of other illicit drugs. These epidemiological data will help NIDA to plan future research strategies.

Studies of factors that put an individual at risk, or vulnerable for drug abuse, as well as factors that are found to protect an individual from vulnerability to drug abuse, can lead to prevention strategies. For example, NIDA-supported investigators found that non-escalating drug use often results from social, situational, and environmental factors, but drug abuse in higher quantities and frequencies often results more from biological, psychological, and psychiatric factors. Studies also show that although drug abusing behaviors can result from multiple causes, many of these factors can be identified early in a high-risk individual's life making prevention possible.

In the future, NIDA will increase its emphasis on the analytic investigation of processes and factors associated with drug abuse, and focus on variations in the patterns of drug abuse, as well as the progression from drug use to drug abuse, dependency, or discontinuation.

Prevention programs seek to identify early in life those protective factors that can increase resiliency and may reduce the onset of drug use, and the progression to abuse, and to test intervention models that inhibit drug use behavior. Both school-based, and comprehensive community based prevention programs are currently being tested. Future goals of NIDA research are to assess the effectiveness of drug prevention efforts in primary health care settings, target culturally diverse groups for prevention programs, develop more effective approaches for rural areas, and identify those components of prevention programs that seem to have the greatest impact in different population subgroups, developmental stages, and environmental settings.

Targeted Population Subgroups

To assure that all segments of the population are served by the treatment and prevention strategies developed at NIDA, subgroups of women and minorities need to be included in targeted studies, with a focus on health and other issues unique to specific populations. Drug abuse is a major health problem for ethnic and minority populations in the United States and often involves more severe consequences for minorities than for nonminorities. For example, minority individuals who abuse drugs are more likely to die, suffer from severe drug-related illnesses, receive inadequate treatment, and be involved in violent disputes and crimes. Factors that lead to drug problems in women may differ from those for men, and prevention and treatment strategies that are successful in men, may not be successful in women. Specifically, a confrontational approach that breaks down denial in a male addict, can decrease self-esteem that may already be at a low level in women, and thus can be counterproductive in treatment of women addicts.

NIDA research seeks to understand gender differences found in drug abuse by focusing broadly on the multifaceted biological, behavioral, and social aspects of gender, rather than solely on the reproductive and maternal roles of women. Basic research sponsored by NIDA indicates that differences in susceptibility to the addictive properties of cocaine may be hormonally-based. For example, results of a NIDA-sponsored study involving male and female rats found that experimentally altering the hormone levels for both the males and females altered the behavioral effects of cocaine, with normal males being the least affected by the drug. Other research has shown a strong relationship between crime and drug abuse for women. Female crime victims who suffered from Post Traumatic Stress Syndrome (PTSD) were 17 times more likely to have major drug abuse problems than nonvictims, and numerous studies have shown PTSD to be a strong potential causative factor for substance abuse.

Subpopulations of Native American, African American, and Hispanic/Latino students have been studied for differences in rates of substance abuse, risk factors, and effectiveness of prevention strategies. Data from the 1994 High School Senior Survey found that trends in drug use by high school seniors were the same for all racial/ethnic groups, although African American students continue to report the lowest rates of use for virtually all drugs. Moreover, since 1989, past year use of LSD was found to double for Hispanic/Latino students, and a greater percentage of Hispanics/Latino seniors than white or African American seniors reported past year use of cocaine. In another study, Native American students living on reservations were found to have a higher level of drug use compared to nonreservation Native American youth and white youth in the same grade levels. A multicultural study of risk factors for early adolescent males has found that family substance abuse, depression, low family pride, peer approval and suicide attempts were related to illicit drug use for Hispanic/Latino and white students but not for African American students. These findings highlight the importance of studies that can identify differences among minority and ethnic groups and subgroups, as they relate to the problems of drug abuse.

Future research goals are to address the need for culturally-relevant research on the factors underlying drug-using behaviors in minority and ethnic subpopulations, to determine how minority populations vary regarding treatment-seeking behavior, and to identify treatment procedures that reflect cultural sensitivity. Drug abuse research targeted to women in the future will include the development of psychotherapeutic, behavioral, and counseling interventions with controlled clinical trials to establish their effectiveness, the investigation of psychological, social and systemic factors that might facilitate or deter women from entering and completing drug abuse treatment, and an examination of the medical, ethical, and legal barriers to including women in clinical studies before, during, and after their childbearing years.

National Institute on Drug Abuse

Intramural Research Program

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
125	$18,650,000	106	$19,230,000	104	$19,805,000	-2	+$575,000

The NIDA Intramural Research Program at the Addiction Research Center (ARC) in Baltimore, Maryland is the largest single drug abuse research program in the world. The ARC conducts interdisciplinary research on the nature of the addiction process; the causes, hazards, prevention and treatment of drug abuse; and the potential of drugs to be abused. Over 100 research projects in the basic neurosciences, clinical pharmacology, and behavioral sciences are conducted yearly. Having an intramural team of scientists allows the Institute to respond quickly to changing patterns of drug use, and the diversity of expertise at the ARC provides an exceptional environment in which to conduct collaborative, challenging, and rigorous drug abuse research.

Funding for the Intramural Program during the last five years has been as follows:

	Amount	FTEs
FY 1991	$17,685,000	127
FY 1992	18,687,000	126
FY 1993	18,687,000	137
FY 1994	18,650,000	125
FY 1995	19,230,000	106

Rationale for the Budget Request

The FY 1996 budget request for the Intramural Program is $19,805,000, an increase of $575,000 over the FY 1995 comparable level of $19,230,000 provided in FY 1995. In FY 1996, total staffing will be 104, compared to 106 in FY 1995.

Highlights of the Intramural Research Program at NIDA include pioneering work in the following areas: treatments for cocaine abuse, including cocaine blockers, cocaine substitution therapies, and behavioral treatments, the identification of less addictive opiate medications, the definition of drug abuse sub-types, and the health consequences of drug abuse.

Treatments for Cocaine Abuse

Development of effective treatments for cocaine abuse and dependence is a NIDA priority. Intramural researchers working together with NIDA Medications

Development Program and extramural scientists and collaborators are using medication and behavioral strategies to target this difficult problem that currently lacks cost effective treatments.

Cocaine Blockers

Intramural scientists are advancing developments of selective cocaine blockers, one major approach to effective anticocaine medications. It is theorized that cocaine euphoria results from its binding to dopamine transporters, molecules that usually work to reabsorb dopamine used as a chemical messenger in brain reward pathways. Effective cocaine blockers must both prevent cocaine from binding to this transporter and allow the transporter to reabsorb dopamine. Intramural advances in cloning the transporter gene have allowed molecular modeling and studies of how changes in the transporter molecule affect its function. These studies have provided the first direct evidence that the transporter recognizes cocaine and dopamine differently and identified specific areas of the transporter that provide targets for selective cocaine blockers. In current studies, intramural scientists are identifying lead compounds that block cocaine analog binding with only small interference with dopamine uptake, and are designing improved compounds of even greater selectivity to provide powerful new weapons to block cocaine effects in cocaine abusers.

Cocaine Substitution Therapies

Clinical observations suggest that the rates at which abused drugs occupy their sites of action in the brain are crucial to the subjective experience of drug euphoria. Substitution therapies for nicotine and opiate addiction take advantage of these differences; slow-delivery forms of compounds acting at the appropriate receptors provide significant treatment benefits. However, little research documents precisely how rates of action affect the euphoria and abuse liability of cocaine and related drugs. Intramural scientists are now conducting investigations to determine the effects of rate of cocaine administration on the euphoric properties and cardiovascular consequences of this drug. These studies will allow determination of rates of occupancy of the dopamine transporter that could produce modest euphoric and cardiovascular effects, and yet block action of further doses of self-administered cocaine. Compounds that acted to occupy these receptors at this rate could thus serve to treat cocaine abuse in a fashion similar to that for methadone maintenance for heroin addicts. Intramural scientists are using cocaine analog structure-function studies to develop long-acting compounds with varying rates of onset that will provide good candidates for effective cocaine substitution medications.

Behavioral Treatments

Developing effective behavioral treatments for cocaine abuse and targeting them to individuals in whom they are likely to work is a major goal for treating cocaine abuse. Intramural scientists have documented the effectiveness of voucher-based reinforcement contingency management. Abusers with antisocial personality were unresponsive to this intervention. Further research will optimize effectiveness and cost-effectiveness of behavioral anti-cocaine therapies.

Identification of Less Addictive Opiate Medications

Intramural scientists seek to develop less addictive medications for pain and opiate addiction. Following studies that identified the gene encoding the principal receptor for morphine and heroin analgesia and reward, the mu opiate receptor, studies of mutant receptors documented for the first time that the receptor's activation by addicting opiate drugs is different from its activation by the normal brain chemicals that work at the same receptors. These observations form a foundation that may lead to the development of medications for pain and opiate addiction that will themselves be less addictive.

Definition of Drug Abuse Sub-types

Scientists in NIDA's intramural program search for explanations of different outcomes resulting from drug use. Some people show an increased vulnerability to drug dependence while others show an increased vulnerability to other health consequences -- (cardiotoxicity, neurotoxicity) -- of drug use. Drug abusers are also differentially affected by comorbidity to mental illness. Current research is attempting to identify sub-types of drug abuse that are differentially susceptible to drug consequences and to determine if these consequences are due to genetic or environmental influences. One sub-type has been recently identified that is predominantly genetically determined and may explain the comorbidity that exists between drug abuse and mental illness.

Health Consequences of Drug Abuse

Drug abuse can have serious health consequences for individuals, their families, and society in general. Drug abusers have much higher rates of morbidity and mortality than individuals in the general population. This not only accounts for much personal suffering but it increases national health care costs as well. Needle sharing and promiscuous unprotected sexual behavior, often associated with intravenous drug use, are major risk factors in the transmission of HIV infection. Current studies in the intramural program are comparing the health status of identical twins who are discordant for drug abuse to assess the impact of drug abuse on general health, including neurological, cardiovascular, psychiatric, and molecular biological functioning. Other studies are comparing the effects of drug abuse on memory and cognitive functioning.

National Institute on Drug Abuse

Research Management and Support

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
261	$24,324,000	280	$24,721,000	278	$25,432,000	-2	+$711,000

This activity provides the resources for the scientific leadership and overall management and direction of the Institute. Funding for Research Management and Support during the last five years has been as follows:

	Amount	FTEs
FY 1991	22,255,000	248
FY 1992	23,871,000	292
FY 1993	24,487,000	287
FY 1994	24,324,000	261
FY 1995	24,721,000	280

Rationale for the Budget Request

The FY 1996 budget request for Research Management and Support is $25,432,000, an increase of $711,000, or 2.9% over the $24,721,000 provided in FY 1995. In FY 1996, total staffing will be 278, as compared to 280 in FY 1995.

The Office of the Director plans and directs all NIDA activities, coordinates programs in targeted populations research, and provides oversight of Equal Employment Opportunity programs. The Office of Planning and Resource Management provides financial, personnel, information resources management, administrative services, and grants and contracts administration. The Office of Extramural Program Review coordinates the scientific review of grant and contract applications. The Office of Science Policy and Communications directs the science planning process, and performs information transfer and research dissemination functions.

Four program divisions--Basic Research, Clinical and Services Research, Epidemiology and Prevention Research, and Medications Development--are responsible for planning and administration of the Institute's extramural research activities.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Detail on Full-Time Equivalent Employment

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director..........	19	19	19
Office of Planning & Resource Management...........	59	59	58
Office of Extramural Program Review................	33	33	32
Office on AIDS..................	2	3	3
Division of Basic Research......	22	26	26
Division of Clinical & Services Research......................	38	39	39
Division of Epidemiology & Prevention....................	22	30	30
Office of Science Policy & Communications................	32	34	34
Medications Development Division	34	37	37
Addiction Research Center.......	125	106	104
Total, NIDA.................	386	386	382

Average GS/GM Grade	
1991............	10.6
1992............	10.7
1993............	10.9
1994............	10.9
1995............	10.9
1996............	10.7

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute on Drug Abuse
Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-5	2	2	2
ES-4	6	6	6
ES-2	1	1	1
Subtotal	9	9	9
Total - ES Salary	$969,266	$1,021,500	$1,031,400
GS/GM-15	50	50	50
GS/GM-14	79	79	78
GS/GM-13	46	47	46
GS-12	35	37	36
GS-11	21	21	21
GS-10	1	1	1
GS-9	13	13	13
GS-8	12	13	13
GS-7	39	40	40
GS-6	21	24	23
GS-5	5	5	5
GS-4	8	8	8
GS-3	3	3	3
Subtotal	333	341	337
Grades established by Act of July 1, 1944 (42 U.S.C.207):			
Ungraded	36	36	36
Total permanent positions	335	335	331
Total positions end of year.	378	386	382
Total full-time equivalent (FTE) employment, end of year	386	386	382
Average ES level	4.0	4.0	4.0
Average ES salary	107,696	113,500	114,600
Average GS/GM grade	10.9	10.9	10.7
Average GS/GM salary	46,399	48,600	50,000

WEDNESDAY, MARCH 22, 1995.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DR. DONALD A.B. LINDBERG, DIRECTOR
KENT A. SMITH, DEPUTY DIRECTOR
DR. HAROLD M. SCHOOLMAN, M.D., DEPUTY DIRECTOR FOR RESEARCH AND EDUCATION
KENNETH G. CARNEY, EXECUTIVE OFFICER
SUSAN U. LEVINE, BUDGET OFFICER
DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. BONILLA [presiding]. We now have the National Library of Medicine, Dr. Lindberg.

Dr. LINDBERG. I'm Dr. Donald Lindberg, Director of the National Library of Medicine.

Mr. BONILLA. Welcome, Dr. Lindberg.

INTRODUCTION OF WITNESSES

Dr. LINDBERG. Thank you, Mr. Bonilla. I should introduce my colleagues. At the far end is Mr. Ken Carney, our Executive Officer, who will retire after 42 years in the Government so this will be his last hearing. Next is Dr. Harold Schoolman, our Deputy Director for Education and Research; Sue Levine, our Budget Officer; and Kent Smith, our Deputy Director. You certainly know Dr. Kirschstein and Mr. Beldon, of the Department.

OPENING STATEMENT

Mr. Bonilla, the National Library of Medicine is the biggest medical library in the world, but it is more. It was given the responsibility by Congress to create what we now call the National Network of Libraries of Medicine to exchange scientific information overseas, and to foster creative new ways for American health care professionals and scientists to stay informed, and for patients to benefit from scientific discoveries. For instance, those that we have heard about all day.

I'd like to report just a few examples of relatively good progress in this work during the past year. These have included support of telemedicine research projects, awarding grants for electronic patient records research, and the birth of a computer based visible man. We believe the NLM is fulfilling Congress' intent that the library be a leader in health science communication.

Our MEDLINE literature search system gained its 100,000th registered user in January. Overall usage increased 15 percent to

7 million searches. The MEDLINE network is not only a notable achievement in its own right but it was a precursor of today's "Information Highway". With this in mind, the NLM continues to support Internet connection grants to encourage hospitals and other medical institutions to connect to the Internet.

In January 1994, the Library announced that its four databases containing HIV–AIDS information would be free to all users. Also, two new databases related to health services research joined the NLM online family. A third new NLM database is a collection of 60,000 historical images drawn from the prints and photographs held by the NLM, and this too is retrievable over the Internet.

The principles of the High Performance Computing and Communications Initiative, in which we participate, continue to guide the Library's decisions about many research targets. Last year the Library funded 12 HPCC health care applications, including testbed networks, telemedicine projects to provide consultation to patients in rural areas, and an advanced computer simulation of human anatomy for training via virtual surgery.

In September, the Library made five additional awards to conduct research in clinical medical terminology and vocabularies, automated tools to support collaborative research on the Internet, and Internet research access to electronic medical records. For the past three years, NLM has supported a project to create two three-dimensional computer representations of human beings, male and female.

The Visible Man, introduced December 1, 1994, was created with digitized data compiled from a 39-year-old man who had willed his body to science. The body was imaged from head to toe using CT, MRI and standard x-rays. It was then frozen and photographed in 1800 1 millimeter-thin slices. This is the first time such detailed information about an entire human body has ever been compiled. It also represents a milestone experiment in the general question of representing images on the Internet.

Another area of science intimately tied to HPCC is that of biotechnology. The National Center for Biotechnology, NCBI, a research component of NLM, creates and maintains systems for storing, analyzing and retrieving information on molecular biology, the human genome, and genetics. Its GenBank database is regularly queried by remote users more than 15,000 times a day. NCBI, too, is experimenting with discovery systems that relate images of biological molecules through their genetic sequencing.

The Lister Hill National Center for Biomedical Communications coordinates the development of the Unified Medical Language System (UMLS). This ambitious project aims to help health professionals easily retrieve and integrate information from a variety of electronic sources through use of its representation and understanding of medical meaning. In 1995, the UMLS will see a field trial in 45 VA hospitals, and with scores of civilian collaborators. There will be a total of 500 investigators.

On another topic, outreach to the health science community remains one of the Library's highest priorities. The services offered by NLM, if they are to be of maximum benefit, need to be widely known to physicians and other health professionals. The key to NLM's outreach is the cooperation of the eight regional medical libraries and of the 4,300 members of the National Network of Libraries of Medicine. The set of maps you see before you illustrate the distribution of NLM's library connections, the status of outreach before and after Congress' allocation of outreach funds, and lastly, the improvements in connecting the country's health care professionals to NLM resources.

Yet, the heart of the Library continues to be, as it has been for 160 years, the labor-intensive task of acquiring, cataloging and indexing the world's biomedical literature. Computers now greatly assist in these processes, but highly trained librarians are required to make the system work. NLM just completed a long-range planning panel study of education and adult learning needs for the information professional.

In summary, the Library's emphasis on constantly improving its information products, increasing the ways in which it serves users, and conducting a vigorous outreach campaign to ensure awareness have continued to seem an effective strategy. It is important to note that this progress has not been at the expense of maintaining NLM's collection which remains at the core of the extensively-used national network.

Mr. Bonilla, the fiscal year 1996 request for the National Library of Medicine is in the amount of $136,311,000. Thank you, and I'd be happy to answer questions.

[The prepared statement and biography of Dr. Donald Lindberg follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Library of Medicine

Mr. Chairman, thank you for the opportunity to appear before you today. Remarkable progress in improving biomedical communication is being made by the National Library of Medicine. From supporting telemedicine projects, to awarding grants for electronic transfer of patient records, to the birth of a computer-based "Visible Man"--the NLM is fulfilling Congress's intent that the Library be a leader in many aspects of health science communication. The unparalleled collection of books and journals remains at the heart of the NLM's mission.

NLM's Online Network

The NLM created MEDLINE, the first large-scale, nationally available, online bibliographic database, in 1971. MEDLINE gained its 100,000th registered user in January 1995. It is estimated that additional thousands--no one knows for sure--have access to MEDLINE through compact disk and various other private sector offerings. Fixed-fee and flat-rate plans for accessing NLM online databases are expanding rapidly. There are about 25 in place at present, and many more under consideration. They range in size and scope from the entire National Institutes of Health to individual hospitals, universities, and commercial organizations. The largest university program, the University of Illinois, currently has five sites with a potential of 75,000 users.

The MEDLINE online network is not only a noteworthy achievement in its own right, but it was a precursor of today's "Information Superhighway." In this regard, believing that the Internet is vital as a route of information for the health sciences, the NLM continues to support an "Internet connections" grant program. This is an interagency program with the National Science Foundation that provides grant funds to encourage hospitals and other institutions to connect to the Internet.

Because of such efforts, the Internet today is the fastest growing route of access to MEDLINE and it is at least partly responsible for the remarkable growth in the number of online searches done in 1994--7 million, an increase of 15 percent over 1993. From virtually zero three years ago, some 25 percent of our network users now come to NLM via the Internet. But two other factors were influential in this growth in usage. In January 1994 the Library announced that its four databases containing HIV/AIDS information would henceforth be free to all users, which immediately doubled their use. In addition, two new databases joined the NLM online family: HSTAR and HSTAT.

HSTAR--Health Services/Technology Assessment Research--contains about 1.5 million post-1984 references on research related to health services--cost, access, and quality, including practice guidelines and technology assessment. The other new database, HSTAT--Health Services/Technology Assessment Text--is noteworthy in that it contains not references and abstracts, but the full text of clinical practice guidelines issued by the Agency for Health Care Policy and Research and NIH consensus statements. Further, the AHCPR guidelines are presented in a form for physicians and health professionals, as well as in an abbreviated form written in language understandable by the layperson. This is a considerable departure from the nature of most other databases on NLM's system.

A third new NLM database, one that is retrievable only over the Internet via the World Wide Web, is *Images from the History of Medicine*. This is a collection of 60,000 historical images from NLM's History of Medicine Division that may be viewed using a browser such as Mosaic. The pictures are caricatures, photographs, fine prints, ephemera, portraits, and illustrations drawn from the books and journals held by NLM. The pictures, which may be reproduced as slides or prints, are used by publishers, authors, film producers, and others who require historical illustration.

High Performance Computing and Communications

The principles of the High Performance Computing and Communications Initiative continue to guide the Library as it makes decisions about its programs. In April 1994, the Library funded 12 projects designed to help physicians practice better medicine by utilizing advanced computing and networking capabilities along the "Information Superhighway." The projects are funding HPCC healthcare applications such as testbed networks to share information resources; computerized patient records and medical images; telemedicine projects to provide consultation and medical care to patients in rural areas; and advanced computer simulations of human anatomy for training via "virtual surgery." The projects will also grapple with such thorny issues as how to store, access, and transmit patient medical records while protecting their accuracy and privacy.

The development of a system of computerized medical records is seen as crucial if we are to be successful in applying the latest in computer and communications technology to medical care. Although much work has been done on electronic patient records, no fully satisfactory system exists as yet. In September 1994, the Library made five awards, totaling $1.5 million, to conduct research in such areas as developing clinical medical terminology and vocabularies, automated tools to support health services research, and Internet access to multimedia electronic medical records systems. The Library is funding these projects jointly with the Agency for Health Care Policy and Research.

For the last three years, NLM has been supporting a project to create two 3-dimensional, computer-generated human beings--male and female. The Visible Man, introduced in 1994, was created with digitized data compiled from the body of a 39-year who had willed his body to science. The donor body was imaged from head to toe using CT, MRI, and x-rays. It was then frozen and photographed in 1,800 millimeter-thin slices. The digital photographs were processed in an imaging computer system along with fiduciary marks and data acquired from the radiologic studies. The resulting dataset is immense--15 gigabytes--that would take up to two weeks of uninterrupted Internet time to transmit in its entirety. This is the first time such detailed information about an entire human body has been compiled and there are many envisioned uses of the dataset. For example, it will be a powerful tool for introducing students to the human body, planning surgery, explaining physical processes to patients, and designing artificial joints and other fabricated body parts. The Visible Man was introduced to the world at a meeting of radiologists in Chicago on November 28, 1994. The project is managed and funded by the National Library of Medicine; work was carried out by scientists at the University of Colorado Health Sciences Center in Denver. Comparable work on a Visible Woman will be completed in 1995.

Another area of science that is tied intimately with HPCC is that of biotechnology. The National Center for Biotechnology Information, a research component of the NLM, creates and maintains systems for storing, analyzing, and retrieving information on molecular biology, biochemistry and genetics. Its GenBank database is regularly queried by remote users more than 15,000 times a day. The Center's scientists also develop advanced software tools for analyzing the structure of molecules and compounds.

Another research component, the Lister Hill National Center for Biomedical Communications, is responsible for coordinating the HPCC-related projects described earlier, conducts research in expert systems, medical linguistics, and other aspects of biomedical communications. The Lister Hill Center has created and operates a hands-on laboratory called The Learning Center for Interactive Technology. At this facility the latest interactive programs for medical imaging and teaching in the health sciences are evaluated and demonstrated. Lister Hill Center staff are also coordinating the development of the Unified Medical Language System, an ambitious project whose purpose is to help health professionals easily retrieve and integrate information from a variety of electronic sources.

Outreach

Outreach to the health science community remains one of the Library's highest priorities. The information services offered, if they are to be of maximum benefit, need to be made widely known to physicians and other health professionals. A key to all of NLM's outreach efforts is the cooperation of the eight Regional Medical Libraries and the 4,100 members of the National Network of Libraries of Medicine. Some 50 major exhibits and hundreds of training sessions, workshops, and demonstrations, are conducted annually under the auspices of the Regional Medical Libraries.

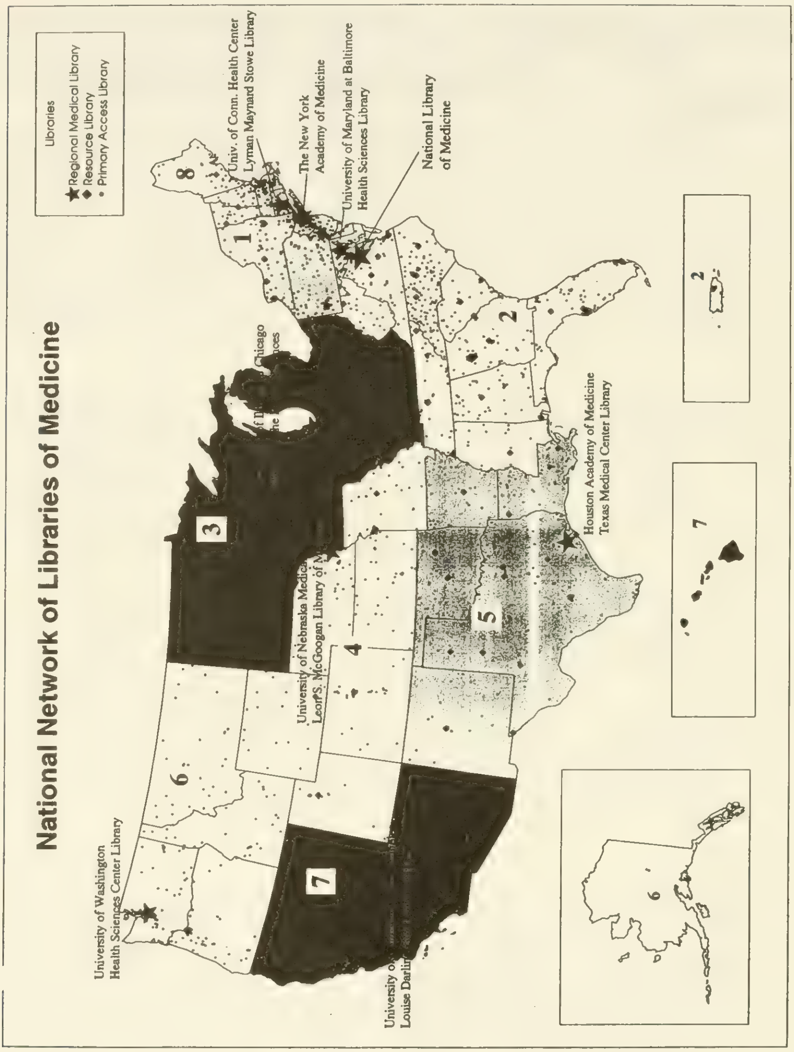
In 1994, a number of NLM's outreach efforts emphasized HIV/AIDS information services. NLM and the NIH sponsored a June 1993 conference on AIDS information services, from which a report with a number of recommendations emanated. One result, as noted earlier, was the decision to make four of NLM's databases containing AIDS-related information free of charge to all users. Other recommendations in the report had to do with reaching out to groups that have not traditionally used NLM's services--public libraries and community groups of various kinds. In September 1994, NLM announced a number of small awards to local organizations that would encourage them to form partnerships and then enable them to purchase computer and telecommunication equipment and to gain training in the use of NLM's databases, as well as other databases.

Basic NLM Services

The heart of the Library's operation continues to be, as it has been for more than 150 years, the labor-intensive tasks of acquiring, cataloging, and indexing the world's biomedical literature. Computers now assist in these processes, but highly trained librarians are still required to make the system work. For example, NLM reference librarians have been helping in the search to identify early published accounts of human radiation experiments conducted under government auspices. It is only because of the Library's comprehensive collections, careful indexing of the literature going back half a century, and the talented staff that this is possible.

In summary, the Library's emphasis on constantly improving its information products, increasing the modes and routes of access, and conducting a vigorous outreach campaign to ensure their widespread use, have proved to be a wise and effective use of taxpayer dollars. It is important to note, however, that this progress has not been at the expense of maintaining NLM's collections, which remain at the core of the extensively used national network.

Mr. Chairman, the FY 1996 request for the National Library of Medicine is $136,311,000. I shall be pleased to answer any questions you may have.


National Network of Libraries of Medicine
Libraries
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Resource Library
Primary Access Library
Univ. of Conn. Health Center
Lyman Maynard Stowe Library
The New York
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University of Maryland at Baltimore
Health Sciences Library
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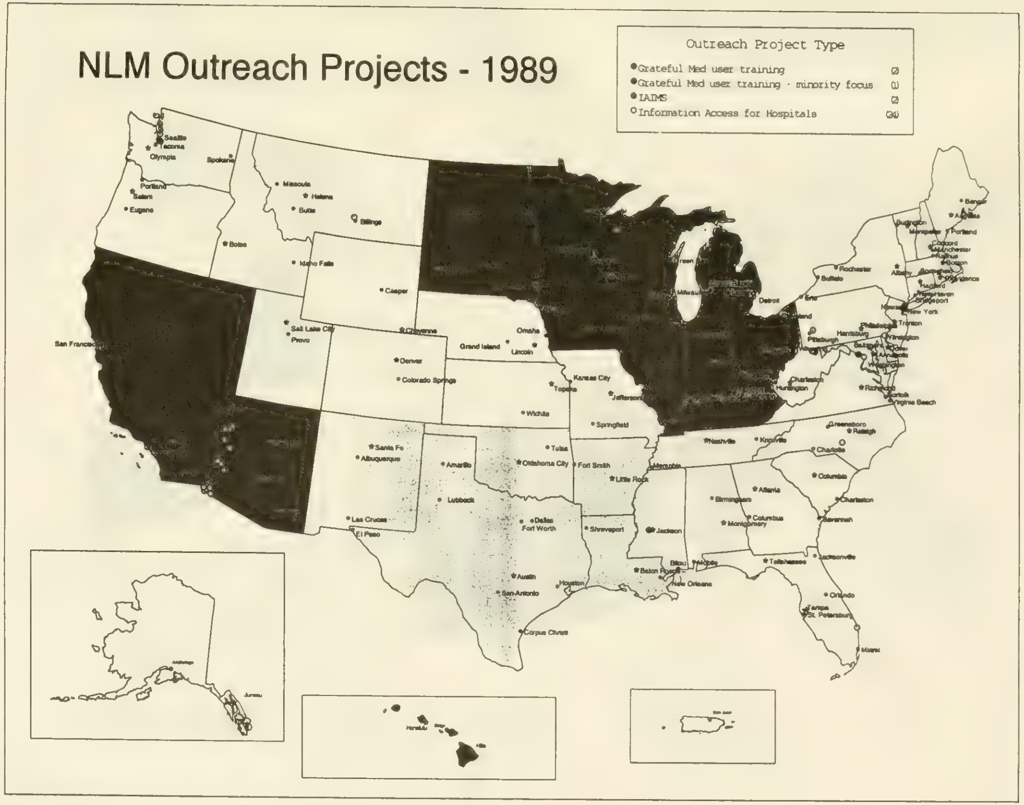
NLM Outreach Projects - 1989
Outreach Project Type
● Grateful Med user training (2)
● Grateful Med user training - minority focus (1)
● IAIMS (2)
○ Information Access for Hospitals (24)
Seattle
Tacoma
Olympia
Spokane
Portland
Salem
Eugene
Missoula
Helena
Butte
Billings
Boise
Idaho Falls
Casper
Salt Lake City
Provo
San Francisco
Cheyenne
Denver
Colorado Springs
Omaha
Grand Island
Lincoln
Kansas City
Topeka
Jefferson
Wichita
Springfield
Santa Fe
Albuquerque
Las Cruces
El Paso
Amarillo
Lubbock
Tulsa
Oklahoma City
Fort Smith
Little Rock
Dallas
Fort Worth
Shreveport
Austin
San Antonio
Houston
Corpus Christi
Memphis
Nashville
Knoxville
Jackson
Baton Rouge
New Orleans
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Atlanta
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Montgomery
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Jacksonville
Orlando
Tampa
St. Petersburg
Miami
Savannah
Charleston
Columbia
Charlotte
Greensboro
Raleigh
Richmond
Norfolk
Virginia Beach
Charleston
Huntington
Pittsburgh
Harrisburg
Philadelphia
Trenton
Wilmington
Baltimore
Annapolis
Washington
Detroit
Milwaukee
Erie
Buffalo
Rochester
Albany
New York
Newark
Hartford
New Haven
Bridgeport
Boston
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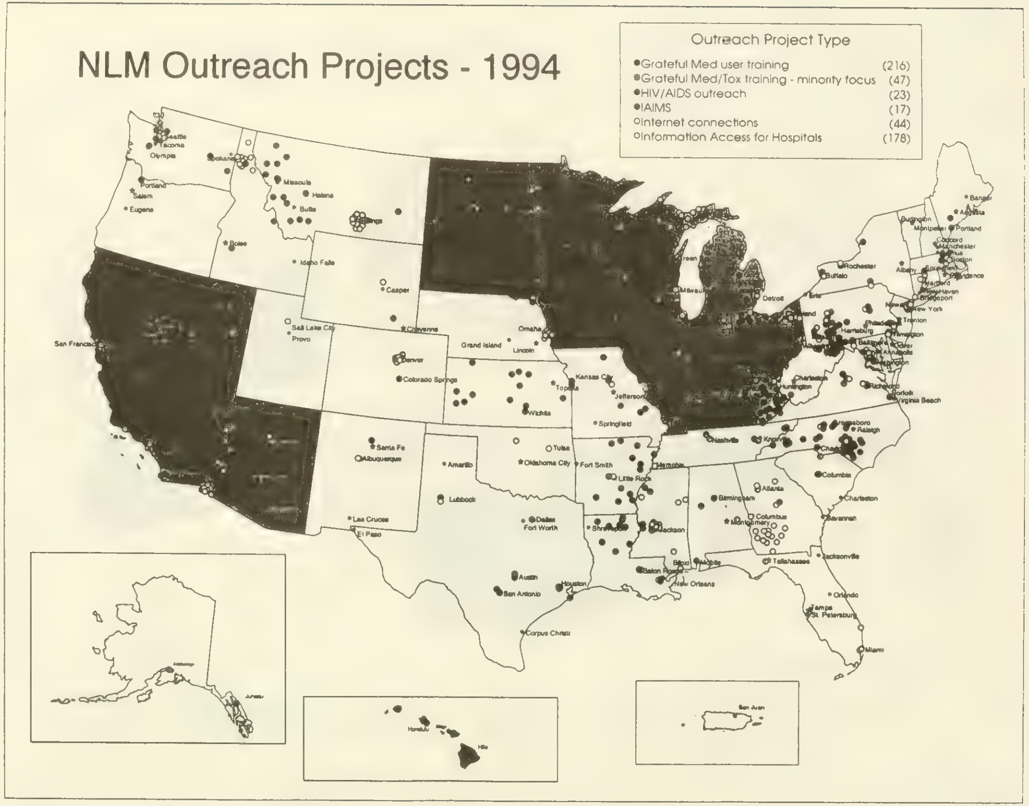
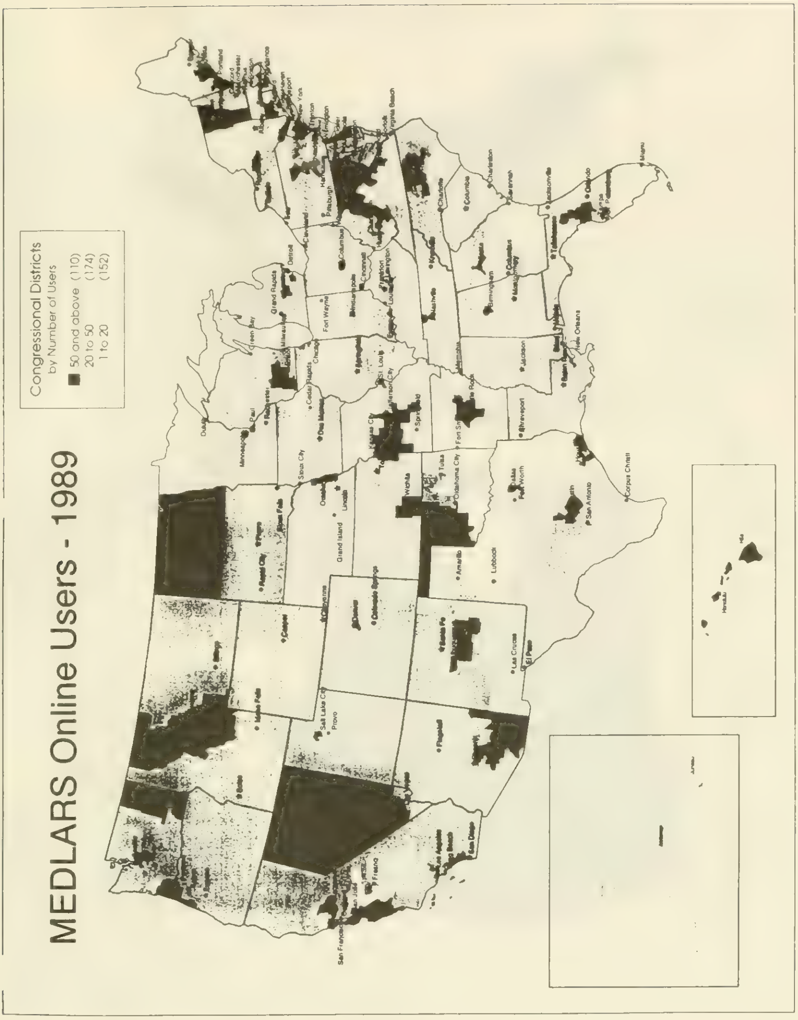
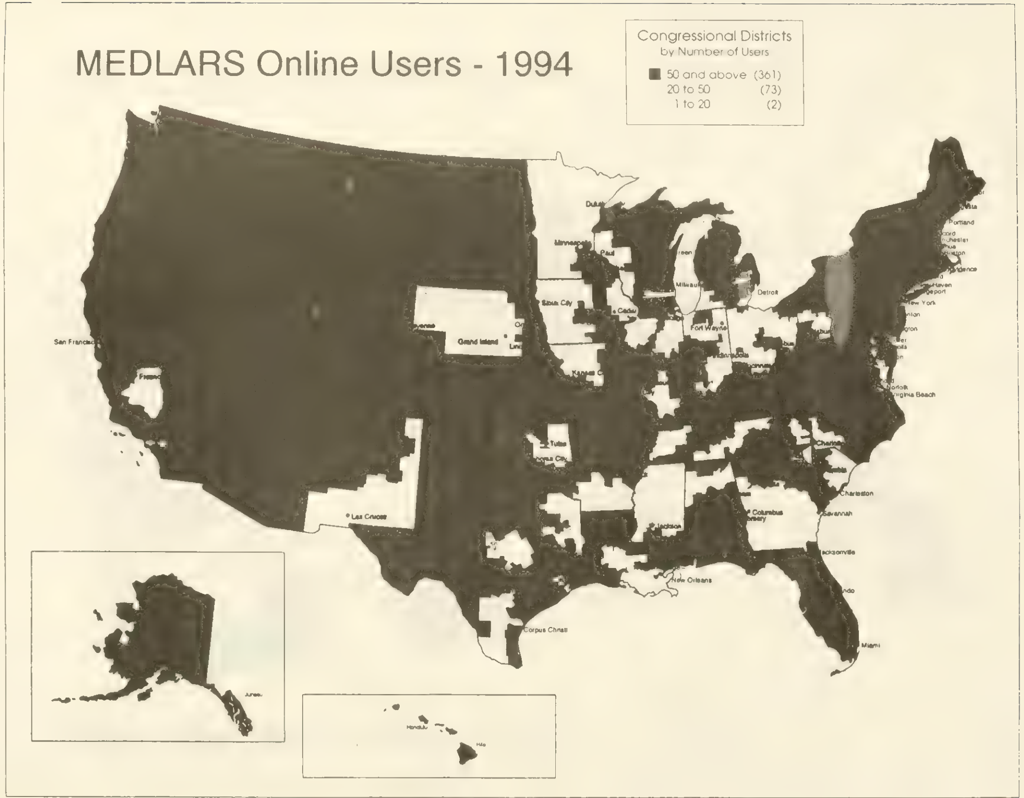
Bangor
Anchorage
Juneau
Honolulu
Hilo


NLM Outreach Projects - 1994
Outreach Project Type
●Grateful Med user training (216)
●Grateful Med/Tox training - minority focus (47)
●HIV/AIDS outreach (23)
●IAIMS (17)
○Internet connections (44)
○Information Access for Hospitals (178)
Seattle
Tacoma
Olympia
Spokane
Portland
Salem
Eugene
Missoula
Helena
Butte
Billings
Boise
Idaho Falls
Casper
Salt Lake City
Provo
San Francisco
Cheyenne
Denver
Colorado Springs
Santa Fe
Albuquerque
Las Cruces
El Paso
Amarillo
Lubbock
Grand Island
Omaha
Lincoln
Topeka
Kansas City
Jefferson
Wichita
Springfield
Tulsa
Oklahoma City
Fort Smith
Little Rock
Dallas
Fort Worth
Austin
San Antonio
Houston
Corpus Christi
Shreveport
Memphis
Jackson
Baton Rouge
New Orleans
Biloxi
Mobile
Birmingham
Montgomery
Columbus
Atlanta
Tallahassee
Jacksonville
Orlando
Tampa
St. Petersburg
Miami
Savannah
Charleston
Columbia
Nashville
Knoxville
Greensboro
Raleigh
Charlotte
Charleston
Huntington
Richmond
Norfolk
Virginia Beach
Milwaukee
Detroit
Erie
Buffalo
Rochester
Albany
Harrisburg
Philadelphia
Trenton
Newark
New York
Bridgeport
New Haven
Hartford
Springfield
Providence
Boston
Nashua
Manchester
Concord
Burlington
Montpelier
Portland
Augusta
Bangor
Anchorage
Juneau
Honolulu
Hilo
San Juan



MEDLARS Online Users - 1989



MEDLARS Online Users - 1994

BIOGRAPHICAL SKETCH

DONALD A. B. LINDBERG, M.D.

Donald A. B. Lindberg, M.D. is Director of the National Library of Medicine, the world's largest library of the health sciences. He was appointed to that position in 1984. From 1992 to 1995 he served in a concurrent position as Director of the National Coordination Office for High Performance Computer and Communications in the Office of Science and Technology Policy, Executive Office of the President.

In addition to an eminent career in pathology, Dr. Lindberg has made notable contributions to information and computer activities in medical diagnosis, artificial intelligence, and educational programs. Before his appointment as Director of the National Library of Medicine, Dr. Lindberg was Professor and Chairman of the Department of Information Science at the University of Missouri School of Library and Information Science, and Professor of Pathology and Director of the Information Science Group at the University of Missouri School of Medicine. He has current academic appointments as Clinical Professor of Pathology at the University of Virginia and Adjunct Professor of Pathology at the University of Maryland.

Dr. Lindberg was elected the first President of the American Medical Informatics Association (AMIA) and, since 1992, he has been a member of the AMIA Board of Directors. He has been called upon to serve on many boards, including the Computer Science and Engineering Board of the National Academy of Sciences, the Symposium on Computer Applications in Medical Care, the American Association for Medical Systems and Informatics, the Organizing Committee for MEDINFO 86, the National Board of Medical Examiners, the Institute of Medicine Advisory Council of the National Academy of Sciences, and the Advisory Council of the International Hospice Institute.

Dr. Lindberg is the author of three books, several book chapters, and more than 150 articles and reports. He has served as editor and editorial board member of nine publications, including the Journal of the American Medical Association.

Dr. Lindberg graduated Magna cum Laude from Amherst College and received his M.D. degree from the College of Physicians and Surgeons, Columbia University. Among the honors he has received are Phi Beta Kappa, Simpson Fellow of Amherst College, Markle Scholar in Academic Medicine, Surgeon General's Medallion, the first AMA Nathan Davis Award for Outstanding Member of the Executive Branch in Career Public Service, the Walter C. Alvarez Memorial Award of the American Medical Writers Association, the Presidential Senior Executive Rank Award, the Outstanding Service Medal of the Uniformed Services University of the Health Sciences, *Federal Computer Week's* Federal 100 Award, Computers in Healthcare Pioneer Award, and honorary doctorates from Amherst College, the State University of New York at Syracuse, and the University of Missouri-Columbia.

OUTREACH

Mr. BONILLA. Dr. Lindberg, this map you were referring to is impressive. You can just flip it over and see how red it's become, covering my entire 58,000-square-mile district in south and west Texas. Providing all this good information to rural doctors is a tremendous service.

Isn't the access to this information an important factor in retaining health care providers in rural communities? Have you had much feedback on that?

Dr. LINDBERG. I've had about 24 years of feedback on that in the State of Missouri. I think you're absolutely correct. The feeling of being utterly isolated professionally drives doctors out of rural communities. And in contrast, the sense of being connected, even if it's only electronic, helps to keep them there.

Many of the ideas of telemedicine were popular and valid back in 1965 to 1975 when Regional Medical Programs were tried in the U.S. Those concepts in part were aimed at just what you said, recruiting and keeping health care professionals in rural areas. They probably were a little bit ahead of their times in that the technology was effective but terribly expensive. You now find that with the Internet, satellite communications and high performance computing systems, telemedicine experiments are probably more realistic.

There are of, course, experiments in Texas specifically. One of the more interesting ones is in a sense a little low-tech, in that there is a circuit-riding librarian, a wonderful lady, who operates out of San Antonio throughout the Rio Grande Valley and serves some 14 hospitals. What she really does is to bring a portable laptop computer, take queries, run them back and forth to NLM and show others how to build up that resource. Although it's a return to an older solution, it is successful.

Mr. BONILLA. I have met her.

Dr. LINDBERG. Have you?

Mr. BONILLA. She does a lot of good work out there.

I have some other questions, Dr. Lindberg, that I'll just submit for the record, and I appreciate your being here today and it was a pleasure to hear from you.

Dr. LINDBERG. Thank you very much.

Mr. PORTER [resuming]. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Lindberg, nice to see you again.

Dr. LINDBERG. Thank you, sir.

INFORMATION SUPERHIGHWAY

Mr. STOKES. Doctor, with respect to the Information Superhighway Initiative, what progress has been made since you were last here? What opportunities do you see on the horizon and what major opportunities would be exploited at the fiscal year 1996 budget request?

Dr. LINDBERG. We find that the Library's natural outreach program is aided and abetted by the supercomputer system and the Internet, because it helps us to connect to and serve remote and rural areas. So the two really for us go together very well.

In the case of the outreach program, we have a top priority to serve health care professionals and our second priority to serve the public. And in both cases, special efforts really are directed toward what we consider to be medically underserved populations. There are five parts of our program. We've upgraded the number and the quality of our presentations at professional meetings, we now do 64 a year. There have been a number of community-based grants, some 275 as one of the maps shows. An example are grants through unaffiliated nurses recently in some five states.

I think an important part of what we're doing is in the special area of toxicology and the environment. There, there are a number of parts of the program, but I think the most interesting is an activity at nine Historically Black Colleges and Universities. This was actually started by Dr. Melvin Spann, who now is head of NLM's Special Information Services Division. That was aimed at being certain that the faculty of HBCUs health schools, those nine, had access to our information and knew how to use it and had connections. That worked quite well over a period of three years, and there are now 44 additional HBCU schools that are getting the same benefits, so to speak, but with monies from the Agency for Toxic Substances and Disease Registry. We are working jointly with them.

There's a new part of that project that has to do with what's called environmental justice. Here the Office of Environmental Justice, that's technically part of EPA, works on that project along with us, CDC, and ATSDR in bringing information to health care professionals. There's a special AIDS program initiative and we have an Adopt A School Program that infuses modern communication systems into a local D.C. high school.

In the end, we've multiplied by five the number of health care practitioners in the last five years that have accounts with NLM and do searching. The map is pretty red, meaning there's connectivity. The quality of all connections isn't as good as we hope it will be in five to ten years.

Mr. Gore, for example, talks about his grandchildren doing their homework with information from the Library of Congress at the kitchen table. Well, we're not quite at that stage yet. But we can get medical information, if it isn't too voluminous and it doesn't involve too many pictures and too high a refinement and too many colors to most practitioners over most parts of the country now.

DISEASE TREATMENT

Mr. STOKES. To what extent are health professionals capitalizing on the information that they can acquire from you with respect to prevention, diagnosis, and treatment of diseases?

Dr. LINDBERG. Well, I think it's the most important question that I face. We know a great deal about those who use us and not as much about those who don't. But we think that we now serve about 25 percent of all American health care professionals directly. Possibly another 25 percent are served well by commercial sources that we don't have direct contact with. Our databases are licensed to some 100 firms and universities. So the effect of NLM spreads quite rapidly from Washington.

I think that we're doing a good job with getting ten training grants, in ten of the advanced medical schools. But we have to keep up a steady campaign to be sure that individual physicians and health care professionals are able to do their own searching. That's really our major push. I guess that's comparable with some kind of a treatment for drug addiction. You like to get them addicted to information on computers.

VISIBLE HUMAN PROJECT

Mr. STOKES. Very good. You mentioned your Visible Man project, and I understand that you have a Visible Female project that's expected to be completed this year, is that correct?

Dr. LINDBERG. That's right.

Mr. STOKES. How wide a usage are you expecting of both the Visible Man and Visible Female?

Dr. LINDBERG. Well, I understand the question, and it's a curious thing, because we didn't go into it impulsively. We had careful study of the importance of imagery in medicine. Medicine has a tremendous amount of information in the form of images, not just books and journals. So we knew it was important to try the experiment, we knew that the 3–D anatomy was under careful study by at least six to eight American schools. But they are all doing bits and pieces of the problem.

So we were certain that the whole experiment was worthwhile, just because of the need to learn anatomy and surgery. But the use of it now, it's clear, has far, far exceeded that. There have been a thousand requests in the last six weeks for availability to this. A number of these are commercial firms that will make value added products. In addition, of course, the people who are expected to take an interest, are namely the medical schools, the anatomists, and the surgeons.

The female is going to be a somewhat higher resolution; actually, it will be at a third of a millimeter resolution. This is the first time such a thing has been tried. It wasn't at all clear that we could even achieve a 1 millimeter resolution but now we are able to do one-third of a millimeter resolution. So we'll do even better with the female.

I think it will be a distinct milestone, sir.

Mr. STOKES. Very good. Thank you, Dr. Lindberg.

Thank you, Mr. Chairman.

Dr. LINDBERG. Thank you, Mr. Stokes.

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Lindberg, let me apologize for having an appointment that was originally scheduled for after our hearings, and that I needed to take. Let me also thank you for being one of our hosts out at NIH earlier in the year, which I think all of the Members found to be extremely helpful.

Dr. LINDBERG. We very much enjoyed your visit.

HIGH PERFORMANCE COMPUTING

Mr. PORTER. I think it's something we ought to do more, much more often, very frankly.

You're stepping down after several years as the director of the high performance computing coordination office. From the vantage point of that post, what is your assessment of the progress of this effort Government-wide?

Dr. LINDBERG. Oh, I'm very enthusiastic about it. I had only agreed to do the job for one to two years, and the two years was up last September, so I'm definitely not stalking off mad. I'm full of enthusiasm for the work. We set certain technical goals, and those goals will be achieved on time or ahead of schedule, namely for faster computers and faster communication lines to connect the whole country. And those two objectives will be clearly achieved. And so from that R&D work, the biomedical people are almost purely beneficiaries, that is to say, we're not proposing to teach the physicist how to design circuits and so forth. We're proposing to have good medical applications.

But the work has started a second phase in which there is a more formal commitment to what's called the National Information Infrastructure, NII, or what the magazines call the electronic highway, and some applications to go on it. The Congress has considered that, as you know, in a bill that has actually passed both the House and the Senate separately, but not jointly. But I think in all versions of the bill, the application areas mentioned include health care high on the list.

So again, I think that if it was important when I jumped into it, it's even more important now that I've left. Because one of the main focuses and one of the main beneficiaries will be health care, and those of us who work in the field, and the public that benefits from it.

USER FEES

Mr. PORTER. I've asked everybody a tough question today, so don't take this personally. With current fiscal constraints, Members of Congress are scrutinizing many programs to see if alternative financing would be possible. How would you respond to the question that if NLM provides information and services that the outside community finds useful, why can't it rely on user fees for its support?

Dr. LINDBERG. I think I can respond to that. I mean, it's a difficult but also an easy question in a way. This particular committee has always urged that NLM recover 100 percent of the marginal costs of access to these databases. So everyone in the U.S. who uses the system, MEDLINE system, does in fact pay for 100 percent of the marginal costs of access. That is to say, the appropriation pays to create the file, because we have to have a file to maintain a library.

But everyone pays his or her total 100 percent fair share to access those files. Users from overseas who didn't have the privilege of paying American taxes pay an additional 15 percent surcharge. So total collections are around $12.5 million a year.

[CLERK'S NOTE: Subsequent to the hearing, the surcharge paid by overseas users was corrected to 25 percent.]

In former years, we returned to the Treasury unused, after paying our expenses, $4 to $6 million a year. In the last few years, the feeling has been I think both from the committee and its staff and our outside advisors, that it would be wise to recover only mariginal costs rather than full access cost. We weren't pricing outrageously high or low, but rather middling. So we are now able to reduce the charges such that the small collections now are somewhat in excess of our costs, but only by a million or two dollars a year. So we are actually returning money to the Treasury still. But that will never get services delivered to medically underserved areas. I mean, it still takes special efforts and outreach if we really want to serve everybody.

Mr. PORTER. I'm afraid what I thought was a difficult question you hit over the fence. [Laughter.]

HUMAN GENOME

Mr. PORTER. One of the early concerns with the Human Genome Project was the tremendous amount of data it would generate, and whether adequate information systems existed to organize and disseminate it. With genome mapping in high gear and the request for genome data increasing exponentially, are you going to be able to keep up with the new data flooding in and the requests to access it?

Dr. LINDBERG. Yes, that really is a serious concern. The lucky thing is that the young man directing the National Center for Biotechnology Information, Dr. David Lipman, has done a remarkably fine job in creating more and more clever algorithms, the formulas that let this be done. So at the moment, they're keeping up. And they think they know a way to keep up with perhaps ten times the data flow that they're currently getting. They can see that far ahead. The actual plan that Dr. Watson originally put forward and Dr. Collins, I think, is still sticking with, would say that the data flow will increase by a thousand times. And I don't think anybody knows how to do that.

So it is still the case that we have to be sure that the research and the information systems continue. But they're doing a very, very fine job, so I imagine, even though they don't know how they'll do it, that they'll find a way to do it.

One of the things that helps, of course, is that a lot of the data now is being contributed by the authors. And so they have ways that can be done using Internet. The second thing is that the big sequencing centers have data acquisition systems themselves and NCBI has made special arrangements so those come directly to them in big blocks, if you will, large number sequences, but small transaction numbers.

Then Merck Corporation has undertaken to do these special analyses and send those directly to NCBI. So I guess the bottom line is at the moment, they're keeping their heads above water, and they think they can see the next few years ahead, and beyond that, we're going on faith.

BIOETHICS

Mr. PORTER. The conference agreement on the 1995 appropriations bill encouraged you to provide reasonable support for the program in bioethics and bibliographic research. How are you meeting this directive?

Dr. LINDBERG. We've had a very, very fine relationship with Georgetown in doing that work. I've had a number of panels investigate to be sure that they were doing a good and impartial job.

And we've had competitive reviews, grants, which started back in 1974. Why is the Government asking some outside outfit to do this, rather than do it as a Federal agency? I think common sense says that whatever else we're good at in the Government, that bioethics might not be our forte, and it might be reasonable to look outside.

The fiscal review of this is rather interesting. I mean, NLM has supported that work absolutely consistently without fail every year since 1974. And the funding started at $82,000 in 1974. It's projected to go to close to $800,000 in 1996. So I would say that's not evidence of anything but a rather relatively happy relationship.

There are two parts of our support. Initially all of the support was by a competitive research grant, which was recompeted every three, four, five years, and which Georgetown always got very high marks on. After a while, I actually suggested around 1985 that it would be more sensible if we did that part of the support as a contract, because they had just gotten yet one other very high review. But it seemed to me that they were producing BioethicsLine, something that the country had come to rely on, 14 years had proven it wasn't just a research idea, it was a product.

So Ed Pellegrino saw it that same way, and we converted that grant to a contract. So there are two parts, then, of the support. One is a contract to produce BioethicsLine, which is then made available by NLM. The second part is to support what's called a reference center, that is to say, the physical collection of books. And in that case, even legal books and newspapers, legal journal articles, things that NLM doesn't itself hold. It is an important national resource, but we don't want to operate it.

So adding the two numbers together, if we look at 1993, 1994, 1995 and 1996, we come up with a total of $697,000, $798,000, $747,000 and $800,000. So the total support has been increasing and is substantial. And we're satisfied with the products.

ELECTRONIC MEDICAL RECORD SYSTEM

Mr. PORTER. You are working with the Agency for Health Care Policy and Research on developing a computerized medical records system. No one questions that such a system is needed. But even after the system is developed, won't it take a tremendous amount of data entry to convert all the existing patient files to the automated system, and how do you expect to handle the patient confidentiality issues that will arise when records can be accessed through an automated system?

Dr. LINDBERG. Those are two extremely insightful questions. This has been an important research subject for at least 30 years, I personally have worked on it myself. Estimates vary as to why it's taken so darned long, and had so many difficulties. In the High Performance Computer and Communications projects, physicists have identified what they have called grand challenges to computation. And I have suggested that the computer based patient record is a grand challenge in the biomedical arena.

So I think the Government as a whole is taking it a lot more seriously. The Department of HHS, at least at the level of the Assistant Secretary, has put together committee structures which let the various agencies work together on these issues. And I think prime movers are in fact NLM and AHCPR. But as I indicated, the VA are coming to pull on the same rope. And they have 176 hospitals where you can try these ideas out. So their contribution in kind is very substantial for us.

You asked two questions, the first is how do you go convert everything. Actually, I would say that the VA is further ahead than anyone else. So a good bit of their data are already machinable. They are already shared. They already are aware of the privacy issues. For the rest, probably when the systems come in, people will simply start with day one, and not bother to go back. It will be easier to just forget the old records and start with new ones.

Mr. PORTER. So for a while, you'd have people on both systems?

Dr. LINDBERG. Probably will. That's my guess. I mean, there's no reason you couldn't go back and convert. But most other scientific fields have found it wasn't worthwhile. For instance, when they started studying earthquakes, I mean, they've been recorded since back in the days of Herodotus. And all of that cogitating gave no understanding of earthquakes at all.

And when they started to make computer databases and computer maps, they simply made a world of progress inside of 20 years, by throwing away all of that Herodotus stuff and starting in the early 1960s with real data. So I think that's the way it will go in medicine, but I'm not certain.

The privacy part is very interesting. It's apparent that there's a tradeoff. As a patient, most of us would tend to emphasize accessibility as much as privacy. If we have an accident and are brought to an emergency room, we want our data to be available. We don't want it all locked up. So some combination there is required.

One of the agencies in HPCC is the National Security Agency, NSA. And I've learned from them and others that the encryption technology is very strong. It's ample for us to lock up the records and guarantee privacy six ways to Sunday. The problem isn't to develop a technology. The problem is to work it out, and that's why we're sponsoring testbed networks, in real medical settings, in situations in which patients and the health care institution, the doctors, can arrive at some compromise as to how much awkwardness are we willing to put up with to guarantee privacy. Do we want to carry a card or code number? The dollar cost is not so great. It's certainly not going to be more than 1 to 1 and a half percent at most more expensive. But the inconvenience might be considerable.

Mr. PORTER. It will probably be defined by the legal profession more than any others.

Dr. LINDBERG. It's looking that way.

BASIC LIBRARY SERVICES

Mr. PORTER. With all the attention given to high performance computing, does your budget allocate adequate resources to basic library operations, for example, to materials acquisition and preservation?

Dr. LINDBERG. In the case of the materials acquisition, I would say yes. We fell behind in 1994 and I think we're okay in 1995 and 1996. The preservation activity is a bit underfunded. I guess we somewhat underestimated the difficulty getting the job done. But I'm told that we still face something close to 60 million pages of brittle literature in our own collection.

[CLERK'S NOTE Subsequent to the hearing, pages of brittle literature in collection revised to "half of the 60 million."]

The good news, on the other hand, is that NLM got behind a really serious program to talk publishers out of using acid-based paper for biomedical literature. And we have succeeded. I mean, that has been pure jawboning and cost practically nothing. Lois DeBakey chaired the committee that did a good bit of the jawboning, and she's really an expert. So we went from 1 percent of indexed journals when we started the program, to now 67 percent of journals on acid-free paper.

So in the future, the problem will be greatly, greatly diminished, simply by increasing awareness of it. For the past, we've got a big backlog of brittle journals.

UNIFIED MEDICAL LANGUAGE SYSTEM

Mr. PORTER. Finally, how far along are you in the development of the Unified Medical Language system?

Dr. LINDBERG. We're pretty far. There are about 300,000 concepts embodied in the system. I guess I might say just very briefly what it is. We don't want to propose to make a standard language for people to use, but rather, the system imagines that we'll utilize the thesaurus in the formal languages that already exist in medicine—psychiatry, public health and so forth. Then we will build a computer system that understands the meaning of those words in those systems. And the simple example is "heart" and "COR" and cardiac, they all mean the same thing, but you have to tell the computer, otherwise it won't know it. The computer, likewise, wouldn't know that fingers are part of a hand and part of an arm, and so forth. You have to tell those relationships.

How far along are we? The field test that I mentioned is actually going to happen this year, in 45 VA hospitals. There are 500 users of the UMLS right now in different parts of the world, mostly U.S., but also Europe and Asia. I'm not certain how many of them are actually doing patient records experiments. There's a lot of other uses for UMLS besides patient records. But I would say that this is entering the last and final phase, and we're going to really see it through and find it a useful system.

COMPUTER LITERACY

Mr. PORTER. A final curiosity question. Do you find a large number of doctors that are computer literate? In general, are doctors computer literate people or not?

Dr. LINDBERG. I think half and half. I mean, obviously the younger the doctor, the more likely he or she has had experience with computing. But it isn't totally limited to age. I think all of us find that the machines are a bit intimidating until we find some use that we can't do without. And generally speaking, e-mail and composing documents are the hookers. Anyone who's ever learned to use word processing would never, never go back to pencil and paper. I'm sure that William Shakespeare would never go back to a pen. [Laughter.]

The connectivity is so marvelous. Now, to me the interesting part of this whole HPCC and Internet is that it's bringing whole new knowledge representations, like this Visible Human. It's striking how high a resolution it is. I had the opportunity to show it to Dr. Zack Hall, the new NINDS Director. He was astounded at the high resolution of that Visible Human.

So I think we have to be patient with the doctors, and they'll come around and they'll all be good computer users.

Mr. PORTER. Dr. Lindberg, thank you very much for your good testimony today and your very forthright answers to all the questions. We also appreciate your patience and apologize for the delay in our hearings today.

Dr. LINDBERG. Thank you, sir.

Mr. PORTER. The subcommittee stands in recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record:]

Bioethics

Mr. Porter: Provide the history of funding for the bioethics bibliographic data base and center since 1990.

Dr. Lindberg: The history of funding for the Bioethics bibliographic data base and center since 1990 is as follows:

Year	Bioethics/Database	Reference Center	Total
1990	250,000	479,814	729,814
1991	275,000	502,319	777,319
1992	375,268	508,031	883,268
1993	246,706	450,000	696,706
1994	398,338	399,432	797,770
1995	331,000	416,000	747,000
1996	342,000	458,000	800,000

High Performance Computing

Mr. Porter: Identify NLM and NCRR 1994-1996 funding for high performance computing, split into intramural and extramural.

Dr. Lindberg: The NLM and NCRR 1994-1996 funding for high performance computing is as follows:

NLM

	FY 1994	FY 1995	FY 1996
Total	**$26,364,000**	**$31,600,000**	**$39,939,000**
Intramural	$17,501,000	$22,522,000	$30,822,000
Extramural	8,863,000	9,078,000	9,117,000

NCRR

	FY 1994	FY 1995	FY 1996
Total	**$15,800,000**	**$20,300,000**	**$22,300,000**
Extramural	$15,800,000	$20,300,000	$22,300,000

As shown in the above tables, NLM's funding for HPCC differs from NCRR in that the majority of our funding is intramural. NLM, through its "Biomedical Applications of High Performance Computing and Communications" program is funding several intramural telemedicine and computer based patient record projects which will demonstrate and test the use of HPCC technologies to assist primary care providers in outpatient settings. NLM has also employed a unique contract mechanism, the Broad Agency Announcement, to solicit contract proposals for research and development projects related to the health care applications of HPCC technologies. Listed below are a few of the contracts that have been awarded through our Broad Agency Announcement:

The University of Pennsylvania will create and evaluate advanced computer simulations of human anatomic structure which support surgical planning and health professions education is entering its second and final year.

The University of California, San Francisco is assembling a high performance wide area network to transmit neuro-radiology images for consultation, patient monitoring, and shared clinical management. The project will examine the patient outcomes which result from use of digital networks to transmit Computed Tomography and Magnetic Resonance Imaging of the brain and spinal cord.

Indiana University will employ a variety of digital networking technologies to tie together major teaching hospitals with community clinics and pharmacies.

The University of Iowa will use the newly developed state-wide digital network in Iowa for creation of a Telecommunications Health Education Resource Center.

The Oregon Health Sciences University will develop a system for the remote diagnosis of skin lesions in five primary care clinics located in underserved rural areas in Oregon and Kansas.

The West Virginia University will build and evaluate a regional telemedicine system designed to serve primary care providers in rural areas of the state.

Northwestern Memorial Hospital will develop a state of the art hospital network which will be linked to primary care locations in the Chicago Metropolitan area. The goal of the project is to provide routine, networked access to high-value clinical information for physicians and other health care providers in their practice settings.

Also, NLM is continuing it's work on the "Visible Human" project to construct a digital library representing complete human beings at millimeter level resolution. Full use and understanding of the anatomical structures depicted in such libraries require the integration of HPCC technologies with technologies used in medical imaging systems including computed tomography (CT) and magnetic resonance imaging (MRI). Combining this digital image library with efficient rendering algorithms will provide new educational tools for researchers, healthcare providers, students and the lay public. NLM is working with industry and academia to encourage the development of interoperable methods for representing and communicating such electronic images. Currently, NLM is beginning to distribute the Visible Human data in an electronic publication media, and over the Internet; and continuing development for a two dimensional database system which underpins the 3-D display graphics. In FY 1996, NLM will extend the image data distribution and continue testing of the first models for the two dimensional database.

NLM also intramurally funds a program called DXPNET (Diagnostic X-ray Prototype Network) and the DocView (Document Delivery of Internet) program. DXPNET can store and transmit radiology images over the National Research and Education Network. Networking will permit physicians to examine x-rays housed in geographically separated locations and increase collaboration between similarly separated investigators. The DocView program represents a possible model for paperless electronic publication. When completed it will allow a remote user to retrieve images of a document over the Internet, read pages, electronically "bookmark" selected pages, magnify, modify, cut and paste images, and retain selected material in electronic or print formats.

Mr. Porter: Identify 1994-1996 high performance computing funding government-wide.

Dr. Lindberg: The FY 1994-1996 high performance computing funding government-wide is as follows:

Federal Agency	FY 1994	FY 1995	FY 1996
Advanced Research Projects Agency	$298,000,000	$344,000,000	$363,000,000
National Science Foundation	267,000,000	297,000,000	314,000,000
Department of Energy	114,000,000	113,000,000	114,000,000
National Aeronautics Space Administration	111,000,000	131,000,000	131,000,000
National Institutes of Health	57,000,000	68,000,000	78,000,000
National Security Agency	40,000,000	40,000,000	40,000,000
National Institute of Science and Technology	18,000,000	25,000,000	34,000,000
Department of Commerce	11,000,000	7,000,000	16,000,000
Environmental Protection Agency	8,000,000	15,000,000	12,000,000
Department of Education	2,000,000	16,000,000	17,000,000
Agency for Health Care Policy and Research		(7,000,000)*	(8,000,000)*
Veterans Administration		24,000,000	24,000,000
	$926,000,000	$1,080,000,000	$1,143,000,000

*Not included as part of the HPCC President's Budget

Integrated Advanced Information Management Systems

Mr. Porter: How many IAIMS systems have been funded; how many are now receiving planning or implementation grants?

Dr. Lindberg: Since the beginning of the IAIMS Grant Program in 1984, awards have been made to 25 health science institutions for planning, model testing, and/or implementation. The Program was revised in 1992 and grants are now available for IAIMS planning and IAIMS operations. In FY 1995, IAIMS Planning activities are active at eight (8) sites from funds awarded in the current or previous year, and IAIMS Operations activities are active at seven (7) sites from funds awarded in the current or previous year. Currently, IAIMS applications are under review from four hospitals and five academic medical centers.

High Performance Computing

Mr. Porter: One aspect of the Library of Medicine's involvement in high performance computing involves telemedicine. Can you describe your work in telemedicine, particularly for rural areas, and how much funding you have allocated to this effort.

Dr. Lindberg: Telemedicine is the use of telecommunications technology for medical diagnosis and patient care. It involves the use of telecommunications technology as a medium for the provision of medical services to sites that are at a distance from the provider. The concept encompasses everything from the use of standard telephone service through high speed, wide bandwidth transmission of digitized signals in conjunction with computers, fiber optics, satellites, and other sophisticated peripheral equipment and software. In 1995, NLM has allocated $8.4 million to telemedicine projects.

Telemedicine can be divided into three areas: aids to decision-making, remote sensing, and collaborative arrangements for the real-time management of patients at a distance. As an aid to decision-making, telemedicine includes areas such as remote expert systems that contribute to patient diagnosis or the use of online databases in the actual practice of medicine. This aspect of telemedicine is the oldest in concept. Remote sensing consists of the transmittal of patient information, such as electrocardiographic signals, x-rays, or patient records, from a remote site to a collaborator in a distant site. It can also include transmittal of grand rounds for medical education purposes or teleconferences for continuing education. Collaborative arrangements consist of using technology to actually allow one practitioner to observe and discuss symptoms with another practitioner whose patients are far away. This raises important issues of referral and payment arrangements, staff credentialing, liability, and licensure potentially crossing state lines. Two-way work stations which provide smooth digital motion pictures have been integral to the long distance, real-time treatment of patients. As new technology is found, collaborative arrangements are the future of telemedicine.

NLM collects and indexes literature related to telemedicine through its MEDLINE and HSTAR (Health Services/Technology Assessment Research) databases. The NLM is currently preparing a specialized bibliography on telemedicine research for wide-spread dissemination.

In FY 1995, NLM is sponsoring a study by the Institute of Medicine (IOM) of the National Academy of Sciences--just getting underway--that will examine the appropriate criteria for evaluation of the impact of telemedicine on access, quality, and cost of care. The Health Care Financing Administration and the Department of Veterans Affairs are also providing support for the study. We hope that the criteria identified by the IOM can be applied in FY 1997 to evaluations of telemedicine projects supported by NLM and other Federal agencies.

NLM, through its "Biomedical Applications of High Performance Computing and Communications" program, is funding several telemedicine projects. West Virginia University is working with a consortium of institutions to create and evaluate a regional rural telemedicine system. The University of Iowa is using the state-wide Iowa Communications Network to establish a National Laboratory for the Study of Rural Telemedicine. The University of Pittsburgh is implementing a teleradiology system linking the university with outlying hospitals in Western Pennsylvania. The Northwestern Memorial Hospital is working to create information linkages between the hospital and primary care locations in the Chicago metropolitan area. The University of California, San Francisco, is working to validate a neuro-imaging telemanagement operating procedure through a wide-area network. Oregon Health Science University is conducting work in teledermatology across the state of Oregon. Indiana University is linking a major teaching hospital with community clinics and pharmacies in the metropolitan area of Indianapolis.

Several NLM granting programs focus heavily on the networked flow of health information, and grants awarded often have telemedicine goals. Information Access Grants are directed towards small and medium-size health institutions in remote rural areas where outlying institutions can network with a larger site equipped with medical information and library staff. Information Systems Grants support computer and communications networking and integration and connectivity of health care institutions. Internet Connections Grants provide support to health institutions involved in research, education, and patient-care to obtain an initial linkage to the Internet.

Issues important to telemedicine are being addressed in several research projects at the NLM. The Visible Human Project is working to establish the standards needed for linkages between image data and text-based data, so that a print library and an image library can serve as a single unified resource for medical information. The DXPNET project works on problems of image compression, high density storage, high speed transmission, and user-machine interface design. The DocView project investigates end user access to the medical literature in the form of scanned pages of journals and other sources sent over the Internet.

Mr. Porter: How do you coordinate your telemedicine work with that underway at HCFA and the Health Resources and Services Administration?

Dr. Lindberg: The National Library of Medicine, HCFA, and the Health Resources and Services Administration (HRSA) work together to ensure that our telemedicine activities are complementary rather than duplicative and that we benefit from each other's telemedicine efforts. The three agencies regularly exchange information through the HRSA-chaired telemedicine subcommittee of the Health Information Applications Working Group of the Information Infrastructure Task Force's Committee on Applications and Technology. Prior to awarding its HPCC projects related to telemedicine, NLM staff members met with representatives of HCFA's Office of Research to verify that projects to be funded by NLM did not duplicate any existing or planned HCFA awards. HCFA staff members reviewed several highly ranked proposals received by NLM to determine whether co-funding would be appropriate. The excellent reports on telemedicine produced for HCFA by Center for Health Policy Research were very useful to NLM in clarifying the dimensions of this complex topic. HCFA provided machine-readable copies of the reports to NLM, and we make them available via the Internet.

An NLM staff member serves on an advisory group for a current HRSA effort to inventory existing rural telemedicine projects, irrespective of funding source. NLM reviewed the scope of this project to ensure that it did not overlap with study of the appropriate criteria for evaluation of telemedicine projects which the Library has requested from the Institute of Medicine (IOM) of the National Academy of Sciences. HCFA and the Department of Veterans Affairs are collaborating with NLM to support this study. The criteria identified by the IOM should be useful in evaluating telemedicine projects funded by NLM, HCFA, and HRSA, as well as other organizations.

Internet

Mr. Porter: Over the past several years, we have watched as use of the Internet has revolutionized the work of academics, business, and government. How has this broad access to the Internet changed the way you organize the Library's services?

Dr. Lindberg: As more of NLM's current and potential users gain access to the Internet, the Library continues to expand Internet use to improve the delivery of existing services and to develop new services that depend on high speed communications.

NLM's World Wide Web and Gopher servers currently provide access to a wide variety of documents including clinical alerts, fact sheets, bibliographies, training manuals, application forms, license agreements, sample records, and many publications, such as recent technical reports on telemedicine sponsored by HCFA. NLM's servers also point users to interactive applications such as NLM's online catalog and a full-text database of AHCPR-supported guidelines, NIH Consensus Development summaries, and the Guide to Clinical Preventive Services.

From May to December 1994, Internet users transferred 975 different files from several NLM servers a total of 162,237 times. Requests for printed versions of many documents available on the Internet have declined. NLM has discontinued publishing its printed catalogs and some bibliographies because essentially all their intended users have access via the Internet or some other online service.

NLM and many other libraries in the National Network of Libraries of Medicine use the Internet to transmit copies of journal articles requested via interlibrary loan electronically. Despite some technical problems, the demand for this service is increasing rapidly.

The Library has begun to distribute machine-readable MEDLINE data via ftp to some of the organizations that lease the data for inclusion in their online services, CD-ROM products, etc. Ftp distribution is a less costly and labor-intensive alternative to distribution on magnetic tape.

NLM is currently testing a new Internet-based successor to Grateful Med which offers more sophisticated assistance to online searchers using information in the Unified Medical Language System (UMLS). Earlier experimentation confirmed that many intended users had difficulty mounting the large files required by this system in their local environments. The Internet version avoids this problem by providing access to these files on a powerful server at NLM. Much of the software is also resident only at NLM which reduces the need to distribute updates to individual users. This approach depends on the faster communication speeds available on the Internet to provide good response time for users.

Use of the Internet also supports more efficient development and use of specialized research tools. Molecular biologists and biotechnologists with Internet access can use National Center for Biotechnology Information's genetic sequence databases and related software without the overhead of mounting these tools on their local systems. An Internet-based data creation tool allows remote scientists to add data to Genbank more quickly and efficiently. In a similar way the Internet enables remote editing of information in the UMLS Metathesaurus and also allows software developers to gain access to UMLS data without mounting its large and complex files in their local environments. Internet will also ease use of the immense Visible Human database.

One of the most important benefits of increasing Internet use is that it improves NLM's ability to communicate with many of its users. As the Library offers new services via the Internet, it incorporates ways for users to send questions and comments to the NLM staff. Because it is so easy for them to do so, users are more likely to take advantage of this capability than to telephone or write their comments.

Although expanding Internet use offers NLM many opportunities to improve the quality and cost-effectiveness of its services, we must be careful not to disenfranchise existing users who don't yet have access. To this end, the Library is surveying its online users to get a better understanding of their current technology and any plans for enhancements. NLM also continues to collaborate with the National Network of Libraries of Medicine and to offer Internet "connections" grants to facilitate access to the Internet for increasing numbers of our users.

Mr. Porter: Has it required that you adjust your fee structures for access to your information services?

Dr. Lindberg: The availability of Internet has allowed NLM to offer some publications, etc. free of charge to Internet users, since the Library does not pay the cost of the communications incurred by these users. In recovering the cost of access to its online services, NLM spreads the total telecommunications cost across all users. In other words, the telecommunications portion of NLM's charges is the same for all users, despite geographic variation in actual costs. Without this policy, users in some rural areas with few information resources would pay substantially more than users in information-rich metropolitan areas. NLM will continue to monitor the effect that increasing use of the Internet has on its telecommunications costs and will adjust charges accordingly. It remains to be seen how Internet costs will be distributed in the future.

Reinvention Laboratory

Mr. Porter: The Library of Medicine has been designated a "Reinvention Laboratory," and you indicate you are considering many projects to change the way you do business. Could you give us some sense of the changes you are considering, and, specifically, explain the appropriations bill language you are requesting to implement your reinvention efforts?

Dr. Lindberg: For thirty years, NLM has been a leader in developing online retrieval services, application of computer technology to library services, and advanced research and development in medical informatics and biomedical computing. Like other pioneers in the use of computers, NLM is now faced with an array of heavily-used, internally developed computer systems which perform certain functions efficiently, but are ill-suited for effective automated links with newer NLM products and services and with the increasing number of university, medical center, library and hospital systems that provide local information support to NLM's primary users. The outmoded NLM systems also require NLM to allocate scarce resources to routine systems maintenance rather than to the development of new and more user-friendly products and services that can be delivered to users through their local systems.

A rapid transition to a more flexible and powerful software and communications architecture for many of NLM's systems will require the kind of innovation inherent in the concept of a reinvention laboratory. The reinvention laboratory will facilitate its transition from outmoded systems dependent on large and expensive mainframe computers to open hardware and software which will permit the development of new and more user-friendly products and services for its customers. The reinvention laboratory involves a major information system development project. The System Reinvention Initiative has four primary components: the access model, Retrieval Systems, File Generation and Maintenance, and Integrated Library Systems.

NLM has requested in its appropriations bill language, no-year funding and the authority to enter into personal services contracts for its information system reinvention activities. Major information system development projects take years to complete. The life-cycle of the project includes several steps, where each step in a major project could take a year or more to complete. Life-cycle segments include requirements analysis, feasibility and alternative analysis, systems design, equipment/software procurement and computer program development. Each segment of the project is inter-related to the other segments of the system development.

The ability to develop a large system is dependant upon the availability of resources when needed. Since the entire project is an entity which is conceived and implemented in its entirety, its planning can best be accomplished without adding the constraints placed upon it by fiscal year funding. An action should take place in relation to the completion of other portions of the development and may occur either earlier or later than initially anticipated, independent of fiscal year. Fiscal year constraints tend to force the project development into twelve-month cycles and lead to additional constraints in the development of a product. Placing this additional set of constraints on a large project can increase significantly both the amount of time required for completion and the cost of the project since the natural work flow of the project will be constrained by fiscal year funding availability.

High Performance Computing

Mr. Porter: Health care reform is driving health care providers to focus their attention on primary care providers in outpatient settings. How are the HPCC projects helping to facilitate this change?

Dr. Lindberg: NLM, through its "Biomedical Applications of High Performance Computing and Communications" program is funding several telemedicine projects which will demonstrate and test the use of HPCC technologies to assist primary care providers in outpatient settings.

Indiana University will employ a variety of digital technologies to tie together a major teaching hospital with community clinics and pharmacies, providing access to a computerized patient record system, computerized prescriptions, and online medical references. An evaluation phase will assess the cost and patient outcomes, changes which result from the use of sharing medical information between the hospital and the outpatient primary care provider.

The University of Iowa will use the newly developed state-wide digital network in Iowa for creation of a Telecommunications Health Education Resource Center, linking three hospital sites with rural primary care providers to provide improved information services.

The Oregon Health Sciences University will develop a system for the remote diagnosis of skin lesions in primary care clinics located in underserved rural areas in Oregon.

The West Virginia University will build and evaluate a regional telemedicine system designed to serve primary care providers in rural areas of the state.

Northwestern Memorial Hospital will develop a state of the art hospital network which will be linked to primary care locations in the Chicago metropolitan area. The network will support the exchange of patient-specific clinical information between the hospital and primary care location.

Outreach

Mr. Bonilla: The information age is upon us and we are glad that NLM is taking a leadership role in the High Performance Computer Initiative. How will HPCC activities and other more basic services continue to be made available to rural areas?

Dr. Lindberg: Since FY 1990 Congress has appropriated outreach funds to the National Library of Medicine (NLM) to support NLM's efforts in bringing the benefits of its information systems to all American health professionals. Based on the recommendations of the Planning Panel on Outreach that was convened to formulate a plan to guide the Library's efforts, NLM developed a long-term, wide-reaching effort to make health professionals across the country more aware of the medical information resources that NLM provides, to facilitate their access to these national resources, to train them in the use of Grateful Med, and, whenever possible, to link them to local library services.

Some of these outreach projects have focused on improving infrastructure at the local institutional level, in particular, on connecting libraries to the Internet. According to a survey conducted in 1993 by the eight Regional Medical Libraries, 24% of the hospital libraries and 73% of the academic institutions in the NN/LM had Internet access. Value-added networks (VANs) such as Compuserve and Tymnet are also important access points for MEDLINE services. Although users in larger cities are able to use higher communication speeds on VANs, in 24% of cities with VAN access, 1200 baud is still the highest speed, and most rural areas do not have VAN access at all. The latter requires use of a toll-free 800 number provided by NLM for this purpose.

For the past four years, grant funds have also been available to enable health sciences organizations to establish an initial hook-up to the Internet or for extension of an existing connection to additional outlying institutions. The awards have been made through an interagency agreement with the National Science Foundation and build upon NSF's successful program.

Small- and medium-size health sciences libraries, primarily hospital libraries, continue to need assistance in introducing computer technology in their institutions. The majority of Information Access Grants, which are available to single institutions as well as consortia of health-related institutions, provide funding to introduce Grateful Med, DOCLINE and Loansome Doc. Not only do these grants introduce Grateful Med into institutions, but they also bring visibility to the libraries and give them credibility as leaders in the Information Age. Particularly for rural areas the Information Access Grant affords the opportunity for small outlying hospitals to connect to larger hospitals that have professional library staff, broader collections, equipment resources and facilities.

NLM continues to develop new resources and new avenues of access to its resources. Internet and related computer technologies are providing NLM with exciting new opportunities to publicize its activities in new ways and to new audiences. These include online full-text access to AHCPR guidelines and NIH Consensus Development Conference Summaries, as well as other health services research information; and AIDS-related databases, now available free of charge. In addition, NLM is working with NIH to make its information products for the public electronically accessible. All of this is made possible by the advent of new technologies that make use of the Internet for access to the most current information. Tools such as gopher and mosaic enable increasing numbers of people to find health-related information on the Internet.

Mr. Bonilla: The level of sophistication that NLM is achieving is quite impressive. Does this level of sophistication substitute for good old fashioned outreach--or do they complement each other?

Dr. Lindberg: Clearly outreach and high technology advances go hand-in-hand. Under the HPCC Initiative NLM has funded projects that are designed to help physicians practice better medicine by utilizing advanced computing and networking capabilities. The projects are health care applications such as testbed networks to share information resources; computerized patient records and medical images; telemedicine projects to provide consultation and medical care to patients in rural areas; and advanced computer simulations of human anatomy for training via virtual surgery.

To be of maximum benefit NLM's information services, and the increasingly sophisticated healthcare application tools that are being developed, need to be more widely known to physicians and other health professionals. This is the point at which outreach plays a critically important role. Through the many outreach efforts that have been undertaken by NLM, in conjunction with the NN/LM, tens of thousands of health professionals have learned about the Library and the information services it provides and have received training in using the online databases. However, there are still far too many health professionals who are not yet aware that NLM and the NN/LM exist. There is a continuing need to inform health professionals about the existing services and to alert them to new advances that can be of benefit in health care. It is especially important to reach the health professionals who serve rural and minority populations.

Mr. Bonilla: What is the budget for outreach activities through NLM? Is that budget increasing or decreasing?

Dr. Lindberg: NLM's outreach budget has been approximately level for the past five years. The amount budgeted has been as follows:

1992	$6,460,000
1993	$6,544,000
1994	$6,333,000
1995	$6,370,000
1996	$6,537,000

Information Superhighway

Mr. Stokes: With respect to the information superhighway initiative, what progress has been made since you were here last? What opportunities are on the horizon, and what major opportunities would be exploited at the FY 1996 budget request level?

Dr. Lindberg: Major developments in computer and communications technologies are being made to advance U.S. science and industry and to create a National Information Infrastructure. NLM has made significant progress in biomedical applications of computing and digital communications, including research in areas such as biomolecular sequence and structure analysis, medical image reconstruction and processing, and the creation and evaluation of advanced computing architectures in these domains.

The NLM Medical Connection grant program provides "jump start" funding (with NSF) to academic medical centers and health care organizations to allow them to connect to the Internet. Approximately 20 connections grants were awarded in 1994; at full funding levels, approximately 100 grants would be awarded annually.

NLM has a number of programs related to various aspects of health care delivery, including health services research, telemedicine, virtual reality, and testbed networks for health care. NLMs National Information Center on Health Services Research and Health Care Technology (NICHSR) was created to serve this need, and to make the results of health services research, including practice guidelines and technology assessments, readily available to health care practitioners, health care administrators, health policy makers, payers, and the information professionals who serve these groups; to improve access to information needed by the creators of health services research; and to contribute to the National Information Infrastructure needed to foster patient record systems that can produce useful health services research data, in addition to providing more accurate clinical documentation.

Under the NLM HPCC Broad Agency Announcement (BAA), awards were made in FY 1994 in telemedicine. These projects will explore areas such as teleradiology, teledermatology, and patient privacy through data encryption. Other BAA awards are funding testbed networks for linking hospitals, clinics, doctors' offices, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imagery. NLM has funded city-wide networks (Indianapolis, Chicago), area-wide (Western Pennsylvania), state-wide (Iowa and West Virginia), and networks for underserved rural areas (in Oregon and Kansas). The awards total $27 million over 3 years. One of these is to a consortium of West Virginia institutions to install a system that applies advanced networking technologies to delivering health care in both rural and urban areas of the state. The successful outcome of these projects will have obvious implications for containing health care costs while raising the quality of patient care.

In Oregon, an award for $2,769,226 is supporting a comprehensive teledermatology program for remote diagnosis of skin lesions via teleconsultation to underserved rural areas. In Iowa, the Iowa Testbed Network ($7,250,017) will use the newly developed state-wide digital network in Iowa for creation of a Telecommunications Health Education Resource Center, linking of three hospital sites, improved information services for rural healthcare providers, and several telemedicine prototype systems. In Chicago, Northwestern Memorial Hospital is planning for state of the art internal networks in a new medical center complex that will be linked to primary care locations in the metropolitan area ($2,334,852). Both scientific and patient-specific clinical information will travel over the network.

The development of computerized medical records is the focus of five new awards totaling $1.5 million announced this fall by NLM and the Agency for Health Care Policy and Research (AHCPR). The cooperative agreements will address research in areas such as developing clinical medical terminology and vocabularies, automated tools to support health services research, clinical data, and multiplatform Internet access to multimedia electronic Medical Electronic Medical Records System (EMRS). Computer-based patient records are critical to improving the quality and reducing the cost of health care. Much work has been done on electronic patient records, but no fully satisfactory, complete system exists as yet. The new awards will help foster development of working systems suitable for both inpatient and outpatient care, and capable of providing data useful in health services research, including technology assessment and outcomes research.

In FY 1995, we expect to support continuation funding of the ten initial HPCC BAA three-year awards and the five initial cooperative agreements, and fund five to ten new projects via contract, grant or consortia mechanisms.

Mr. Stokes: To maximize the benefits of this technology, is there a significant outreach component, explain?

Dr. Lindberg: High technology advances and outreach go hand-in-hand. Since FY 1990 Congress has appropriated outreach funds to the National Library of Medicine (NLM) to support NLM's efforts in bringing the benefits of its information systems to all American health professionals. Based on the recommendations of the Planning Panel on Outreach that was convened to formulate a plan to guide the Library's efforts, NLM developed a long-term, wide-reaching effort to make health professionals across the country more aware of the medical information resources that NLM provides, to facilitate their access to these national resources, to train them in the use of Grateful Med and, whenever possible, to link them to local library services. Emphasis is placed on teaching those health professionals who provide care to rural, inner city, minority and other underserved populations.

Health professionals serving minority populations have a special set of problems in accessing information. NLM has geared a variety of outreach initiatives to these communities in the belief that direct access to NLM's databases--especially MEDLINE via Grateful Med--can help compensate for the absence of other health resources. To date more than 60 outreach projects have had a minority focus.

In August 1991, NLM initiated a pilot project intended to establish a mechanism to strengthen the capacity of Historically Black Colleges and Universities (HBCUs) to training medical and other health professionals in the use of toxicological, environmental, occupational and hazardous waste information resources developed by NLM. The project followed a number of articles and reports that stressed the disproportionate exposure of minorities to environmental and occupational hazards. Since HBCUs educate most of the nation's minority health professionals, this platform was selected as the optimum medium for disseminating health and environmental information to minority communities. The outreach training initiative that was undertaken has been fully implemented at each of the nine participating HBCUs. Beginning in 1992, NLM began collaborating with the Agency for Toxic Substances and Disease Registry (ATSDR) in Atlanta, Georgia to provide training and free access to other HBCUs and Minority Institutions (MIs) with environmental and occupational health programs or concerns. To date, forty-four additional HBCUs/MIs have been involved in the extended project. The project has significantly impacted the nine institutions involved in the pilot study. Faculty, students, researchers, physicians residents, librarians, and community residents have benefited from access to the NLM databases. Similarly, additional HBCU/MIs have benefited from the free training and database access through the projects extension with ATSDR support. More recently, the Environmental Justice Office of the EPA has offered support to use the training program as the information backbone to the CDC/ATSDR Mississippi Delta initiative.

The Toxicology Information Outreach Project has been further expanded to include training in the use of NLMs HIV/AIDS resources. The impact of AIDS in communities of color is particularly severe. Building upon an existing collaboration with the HBCUs enables NLM to place information in the hands of health professionals working closely with the most heavily affected communities.

In June 1993 NLM hosted the NIH HIV/AIDS Information Services Conference. This conference brought together representatives of five of the major constituencies using or needing HIV/AIDS information--clinical researchers; medical, dental and nursing providers; allied health care providers; news media and the general public; and patients and the affected community. While each constituency indicated unmet information needs, those in the affected community were most expressive in identifying gaps in information services. As a result of feedback obtained from the community, NLM eliminated all online charges for use of its four AIDS-related databases. This was made possible by funds provided by the Office of AIDS Research specifically for this purpose.

NLM also initiated a number of new or expanded outreach efforts in response to the recommendations of the conference. In FY 1994 NLM announced the availability of modest funding to enable local groups to design their own programs for improving information access for patients and the affected community as well as their caregivers and the general public. Far more proposals were received than could be funded. Eighty-nine proposals were received from community based organizations, patient advocacy groups, public and health sciences libraries; funding was available to support nineteen of the projects. Because of the strong response and expressed interest, NLM is planning to support additional projects this fiscal year. It is estimated that FY 1995 funds will support fourteen projects.

Small- and medium-size health sciences libraries, primarily hospital libraries, continue to need assistance in introducing computer technology in their institutions. The majority of Information Access Grants, which are available to single institutions as well as consortia of health-related institutions, provide funding to introduce Grateful Med, DOCLINE and Loansome Doc. Not only do these grants introduce Grateful Med into institutions, but they also bring visibility to the libraries and give them credibility as leaders in the Information Age. Particularly for rural areas the Information Access Grant affords the opportunity for small outlying hospitals to connect to larger hospitals that have professional library staff, broader collections, equipment resources and facilities.

NLM continues to develop new resources and new avenues of access to its resources. Internet and related computer technologies are providing NLM with exciting new opportunities to publicize its activities in new ways and to new audiences. These include online full-text access to AHCPR guidelines and NIH Consensus Development Conference Summaries, as well as other health services research information; and AIDS-related databases, now available free of charge. In addition, NLM is working with NIH to make its information products for the public electronically accessible. All of this is made possible by the advent of new technologies that make use of the Internet for access to the most current information. Tools such as gopher and mosaic enable increasing numbers of people to find health-related information on the Internet.

To be of maximum benefit, however, NLM's information services, and the increasingly sophisticated healthcare application tools that are being developed, need to be more widely known to physicians and other health professionals. This is the point at which outreach plays a critically important role. Through the many outreach efforts that have been undertaken by NLM, in conjunction with the NN/LM, tens of thousands of health professionals have learned about the Library and the information services it provides and have received training in using the online databases. However, there are still far too many health professionals who are not yet aware that NLM and the NN/LM exist. There is a continuing need to inform health professionals about the existing services and to alert them to new advances that can be of benefit in health care. It is especially important to reach the health professionals who are serving rural, minority and other underserved populations.

High Performance Computing

Mr. Stokes: Do we know if the advanced use of computerized technologies is becoming a significant component of the Health Professions Education and Training Curriculum?

Dr. Lindberg: Computerized technologies have traditionally been incorporated in health professions education and training as an adjunct to the primary teaching method. For example, the National Library of Medicine's Computer-based Curriculum Delivery Systems project has produced curricula for the health professions that are currently in use in about 50 health professions schools, where they are most often used to enrich the curriculum. The development of computerized educational resources for the health sciences is actively pursued by both universities and the private sector. NLM's AVLINE database catalogs audiovisual materials and computer programs that have been created for health professions education. The database is updated weekly adding some 190 new records each month to a file that contains over 27,000 records. NLM's Learning Center for Interactive Technology show-cases biomedical educational technologies and is visited regularly by health professions educators. The Center also maintains a database of over 100 authoring tools that allow educators to create their own instructional materials without requiring computer programming expertise.

Perhaps the single greatest influence today on the incorporation of advanced technologies in the health professions education and training curriculum is the extraordinary growth of access to Internet resources through the World Wide Web over the last year. A recent compendium of health sciences multimedia education resources notes that there are currently over 2800 teaching files and some 75 courses or textbooks available on the Internet and that the number of these resources is constantly growing. At the University of Iowa, under NLM funding, the medical school is providing educational materials for health professionals on the Internet as part of their Virtual Hospital World Wide Web application. Continuing medical education credit is beginning to be granted over the Internet. For example, the University of Washington grants CME credit for radiologists, and the Department of Pathology of the Uniformed Services University of the Health Sciences grants CME credit in surgical pathology.

Medical schools are rethinking their curricula and one major component of this process is the central role that technology will play. Efforts are underway by increasing numbers of health professional organizations to encourage their members to make greater use of technology for educational purposes. Many conferences have as their primary theme the current and future role of technology in health professions education, and their organizers often refer to the technology-driven "paradigm shift" that is taking place in health professions education.

Mr. Stokes: What are the anticipated commercializations of this technology?

Dr. Lindberg: Many specialty medical boards and societies are experimenting with ways of using the Internet for the delivery of creditable continuing medical and nursing education programs.

Visible Human Project

Mr. Stokes: How wide a usage is expected of the Library's developed 3-dimensional male and female computer generated human beings? Having completed the development of the visible man and with work on the visible female expected to be completed this year, what is the next phase of this initiative?

Dr. Lindberg: To date, NLM has received over 150 requests to license the Visible Human Data Set. The proposed uses include multimedia educational products for use from kindergarten through post-graduate medical education as well as those designed for the home as a reference and for line-long education, surgical simulators, and a reference set for the calibration of certain clinical and exposure models.

The Visible Human Male has been completed and is being distributed. The Visible Human Female should be completed in the Fall and be ready for distribution in November. This will successfully complete Phase I of the Project.

A public Visible Human Conference will be held in the fall at which participants will present their applications of the Visible Human Data Set, discuss problems and solutions in using the data set, and exchange software algorithms and tools.

The main goal of Phase II will be the task of turning this data set into an interactive intelligent data base. A cadaver specific grid system is being developed in order to locate any object within the data set. This is essential to NLM's pilot in-house project for building such an image data base using the Visible Human Male thorax data as a model.

Opportunities

Mr. Stokes: Please describe the most promising opportunities you see for the Library of Medicine in the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Lindberg: The most promising opportunities are as follows:

Biotechnology Information

NLM's National Center for Biotechnology Information (NCBI) offers a key component of the scientific infrastructure for carrying out molecular biology and biotechnology research. By assembling and distributing the NIH GenBank sequence database and by providing state-of-the-art sequence analysis tools, NCBI assists both academic and industrial scientists in the fast-paced field of gene discovery. NCBI maintains the world's foremost collection of all known DNA sequences, now numbering 230,000 sequences and 237,000,000 base pairs from over 5,000 different species. Over 35,000 sites have accessed NCBI data over the past year and every day some 15,000 queries are processed by NCBI computers, many involving complicated comparisons of single sequences against the entire database. NCBI has pioneered extremely fast and accurate sequence search techniques and as part of the HPCC initiative makes this advanced technology available to the biotechnology and biomedical community at no cost. GenBank has been doubling in size every 20 months and in the coming year will grow even faster with the addition of 300,00 human cDNA clones which will be produced at the Washington University Sequencing Center under an agreement with the Merck pharmaceutical company. The agreement is unprecedented in establishing a project with the express purpose of creating an open, non-proprietary resource to benefit the entire biomedical community in the search for genes responsible for human disease. NCBI's role will be to ensure that these data, as well as the rest of the database, are made immediately available to the public.

Visible Human Project

As part of the NIH investment in High Performance Computing and Communications (HPCC), which are building powerful computers to store and analyze biomedical scientific data and extending high speed computer networks to create a national electronic community of health professionals, NLM is bringing the study of anatomy into the information age by creating the worlds first comprehensive digital record of the human body. The Visible Human Project is acquiring the 3-D digital representation of an entire human being at millimeter-level resolution, derived from computed tomography, magnetic resonance imaging, and digitized cryosections. Highly detailed three-dimensional representations of this first visible human were released nationally via the Internet in November 1994. The next steps will be object classification and making available geometry based image libraries. Potential uses include preoperative planning of surgical procedures, fabrication of implant prostheses, and supplementing the use of real cadavers for teaching in medical schools.

Telemedicine

In Oregon, an HPCC award is supporting a comprehensive teledermatology program for remote diagnosis of skin lesions via teleconsultation to underserved rural areas. In Iowa, the Iowa Testbed Network will use the newly developed state-wide digital network in Iowa for creation of a Telecommunications Health Education Resource Center, linking of three hospital sites, improved information services for rural healthcare providers, and several telemedicine prototype systems. In Chicago, Northwestern Memorial Hospital is planning for state of the art internal networks in a new medical center complex that will be linked to primary care locations in the metropolitan area. Both scientific and patient-specific clinical information will travel over the network. These projects are designed to help physicians practice better medicine by utilizing advanced computing and networking capabilities. Through telemedicine, doctors and other health care providers can consult with specialists thousands of miles away, share medical records and x-rays, and continually upgrade their education and skills. Patients, particularly those residing in rural and other currently underserved areas, will be the ultimate beneficiaries of the use of these advanced technologies.

UMLS

In biomedicine, the disparity in the biomedical terminology used to describe related concepts in different machine-readable files prevents practitioners and researchers from integrating relevant biomedical information from separate sources, such as the biomedical literature, clinical records, medical databanks, and expert knowledge bases. In response, NLM has created and published on CD-ROM a set of Knowledge Sources (the Metathesaurus, Semantic Network, and Information Sources Map) as part of the Unified Medical Language System (UMLS) research effort to link together computer-based biomedical information resources. Plans include further expansion of these Knowledge Sources and applications that use them to enable retrieval of related biomedical information from many sources.

System reinvention

With its System Reinvention Initiative, a key component of NLMs reinvention lab, NLM is seizing the opportunity to replace its legacy systems with scalable new systems offering users a range of enhanced capabilities. The System Reinvention Initiative has four primary components: the Access Model, Retrieval Systems, File Generation and Maintenance, and Integrated Library System. The Access Model consists of all software systems between a user at a workstation or terminal and an NLM database system. The Retrieval Systems are the back end retrieval engines--multiple systems which operate against different types of databases. Retrieval Systems receive queries in language they can understand, and return results. The File Generation and Maintenance project will create a flexible, powerful environment for building, editing and maintaining the files the Retrieval Systems run against. And the Integrated Library System project will use a combination of off-the-shelf software and custom modules specific to NLM's needs to encompass the myriad tracking, processing and circulation-related functions of a great library with collections in the millions of items. Central to the System Reinvention planning process is the concept of increasing availability of Internet access both for information delivery and to facilitate user surveys and feedback which will help NLM refine its offerings and its services.

Mr. Stokes: To what extent will the FY 1996 budget allow the library to begin to implement the opportunities that are ready to be exploited?

Dr. Lindberg: Information technology has at once become the means for advancing the pace of scientific discovery, in fields such as molecular biology, and the means by which health care delivery in the academic medical center, the local community hospital, and the rural clinic can keep pace with rapid advances in the laboratory. If health care practice is to be based on scientific evidence about the outcomes of alternative therapies and different methods of delivering health care, more cost-effective methods of conducting outcomes research and of making the results of research available to health care practitioners at the point of care are necessary.

NLM has a number of programs related to various aspects of health care delivery, including health services research, telemedicine, virtual reality and testbed networks for health care. The successful outcome of these projects will have obvious implications for containing health care costs while raising the quality of patient care.

Research Grants

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000 According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your institute, what has been the trend in success rate over the past five years?

Dr. Lindberg: For research grants the success rate has steadily declined from twenty-three percent in FY 1990 to eleven percent in FY 1994. However, at the same time, the number of research grant applications reviewed has grown from sixty-six in FY 1990 to one hundred sixty-six in FY 1994. In FY 1995, it is expected that the number of new applications may decline, due to the perceived stiff competition and decreased likelihood of support. The number of approved applications in the excellent and outstanding categories may rise as growing numbers of talented young investigators complete medical informatics training.

Mr. Stokes: What has been the trend in the average cost of research grants over that same time period? What is the trend in terms of constant dollars?

Dr. Lindberg: The largest of the extramural research activities is medical informatics. Research project grants in this area had an average total (direct and indirect) cost of $251,500 in FY 1990. In FY 1994, the average cost declined to $168,700. This reflects a relative increase of grants to younger investigators, completion of major projects initiated in earlier years, and careful scrutiny of project budget requests, both by reviewers and by program staff.

Mr. Stokes: What is the success rate for research applications received form minority researchers? From women? From African Americans? From HBCUs?

Dr. Lindberg: The success rate for women applicants is better than the average, approximately twenty-five percent. The number of minority or African American applicants is still very small, one or two a year. There has been only one research application from an HBCU. It has since been funded, but through a different institution.

The only HBCU applicant was Charles R. Drew University of Medicine and Science in Los Angeles. Ramish Patil was the applicant. When an amended application was filed, Patils institution (University of Southern California) was the applicant institution and Drew was the subcontractor. The actual study site is at Drew/King Medical Center.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the avenge costs of research project grants awarded to women? To minority researchers? To African Americans researcher? To HBCUs?

Dr. Lindberg: For the younger women investigators, average costs have been approximately $100,000 per year, with little difference in either current or constant costs. This is in the lower range for the special grant awarded to young scientists, but all these investigators received what they had requested. For more senior investigators, the average award is the same as for other investigators. There is only one funded minority investigator at present; his award in FY 1994 was for $250,000. There have been no African American investigators.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

FY 1996 Budget — Page No.

Organization chart 66
Appropriation language and explanation of language change 67
Language analysis 68
Amounts available for obligation 69
Budget mechanism table 70
Summary of changes 71
Budget authority by object 73
Administrative costs 75
Authorizing legislation 76
Appropriation history 77
Budget authority by activity 78

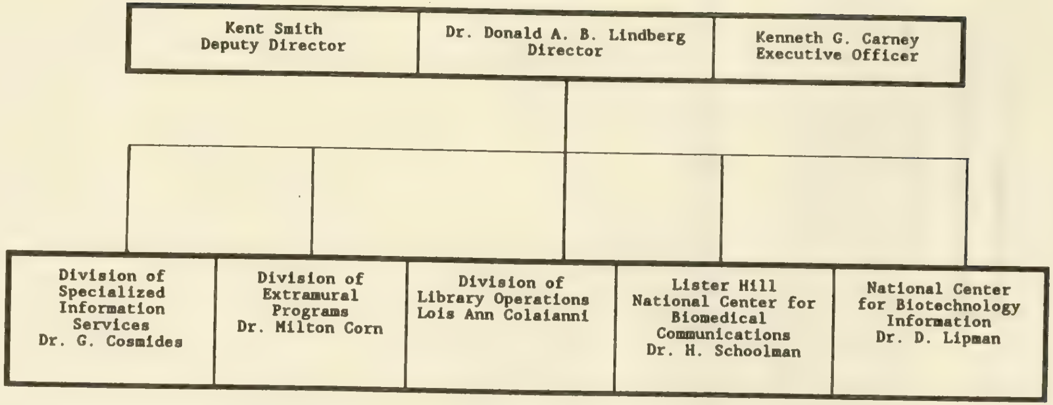
Justification:

A. General statement 79
B. Extramural research 82
C. Intramural research 86
D. Research management and support 95
E. Detail of full-time equivalent employment (FTE) 96
F. Detail of end-of-year employment 97

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Organization Structure


Kent Smith
Deputy Director
Dr. Donald A. B. Lindberg
Director
Kenneth G. Carney
Executive Officer
Division of Specialized Information Services
Dr. G. Cosmides
Division of Extramural Programs
Dr. Milton Corn
Division of Library Operations
Lois Ann Colaianni
Lister Hill National Center for Biomedical Communications
Dr. H. Schoolman
National Center for Biotechnology Information
Dr. D. Lipman

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to the Library, [$126,274,000] *$136,311,000*. Of which $4,000,000 shall be available until expended for improvement of information systems. Provided, That in fiscal year 1996 and thereafter, the Library may enter into personal services contracts for the provision of services in facilities owned, operated or constructed under the jurisdiction of the National Institutes of Health.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Language Analysis

Language Provision	Explanation
"$4,000,000 shall be available until expended for improvement of information systems."	Language has been added to provide NLM needed flexibility in its information system reinvention activities. This will allow procurement actions supporting this multiyear systems development effort to take place without fiscal year constraints.
"the Library may enter into personal services contracts for the provision of services in facilities owned, operated or constructed under the jurisdiction of the National Institutes of Health."	Language has been added to authorize the use of personal services contracts for the information system reinvention activities. This will provide for specialized expertise needed for the duration of the reinvention project.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$119,981,000	$126,274,000	$136,311,000
Rescission in accordance with PL 103-211..............	-1,962,000	---	---
Section 205 Procurement reduction....................	---	-271,000	---
Section 207 Rent reduction.....	---	-2,000	---
Section 513 S&E reduction......	---	-253,000	---
Subtotal, Adjusted Appropriation..............	118,019,000	125,748,000	136,311,000
Comparative transfer to:			
Office of AIDS Research, NIH for HIV Activities..........	-2,782,000	---	---
Subtotal, adjusted budget authority..........	115,237,000	125,748,000	136,311,000
Unobligated balance lapsing...	-236,000	---	---
Total, Obligations..........	115,001,000	125,748,000	136,311,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1994: $11,679,000; FY 1995: $10,618,000; FY 1996: $10,618,000

Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research: FY 1995 $2,946,000; FY 1996: $3,162,000.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Extramural Programs:						
Grants:						
Noncompeting	63	$16,152,000	65	$13,461,000	69	$20,202,000
Competing	64	6,589,000	68	10,869,000	60	6,271,000
Subtotal, Grants	127	22,741,000	133	24,330,000	129	26,473,000
Contracts:						
Noncompeting	8	5,678,000	8	6,151,000	--	---
Competing	--	---	--	---	8	6,323,000
Subtotal, Contracts	8	5,678,000	8	6,151,000	8	6,323,000
Total, Extramural	135	28,419,000	141	30,481,000	137	32,796,000
	FTEs		FTEs		FTEs	
Intramural Programs:						
Library Operations	345	45,208,000	337	48,265,000	336	49,225,000
Lister Hill Center	81	19,560,000	82	24,068,000	80	31,028,000
Biotechnology Center	32	9,166,000	34	9,714,000	33	9,905,000
Toxicology Information	37	4,894,000	36	5,045,000	35	5,144,000
Total, Intramural	495	78,828,000	489	87,092,000	484	95,302,000
Research Management and Support	101	7,990,000	97	8,175,000	96	8,213,000
Total Budget Authority	596	115,237,000	586	125,748,000	580	136,311,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Summary of Changes

1995 Appropriation	$125,748,000
1996 Estimated budget authority	136,311,000
Net Change	+10,563,000

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Programs				
a. Within grade increase		$28,086,000		+$412,000
b. Annualization of January 1995 pay increases		28,086,000		+184,000
c. January 1996 pay increases		28,086,000		+377,000
d. Service and supply fund increase		1,375,000		+38,000
e. Payment for centrally furnished services		9,328,000		+810,000
f. Increased cost of supplies, materials, literature and other expenses		48,303,000		+1,737,000
Subtotal				+3,558,000
2. Research Management & Support:				
a. Within grade increase		5,687,000		+83,000
b. Annualization of January 1995 pay increases		5,687,000		+37,000
c. January 1996 pay increases		5,687,000		+77,000
d. Service and supply fund4 increase		73,000		+2,000
e. Increased cost of supplies, materials, literature and other expenses		2,415,000		+69,000
Subtotal				+268,000

Summary of Changes--continued

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
B. Program:	No.	Amount	No.	Amount
1. Grants:				
a. Noncompeting........	65	$13,461,000	+4	+$5,162,000
b. Competing..........	68	10,869,000	-8	-3,019,000
Total..............	133	24,330,000	-4	+2,143,000
2. Contracts..............	8	6,151,000	--	+172,000
3. Intramural Programs.....	489	87,092,000	-5	+4,652,000
4. Research Management and Support	97	8,175,000	-1	-230,000
Subtotal............				+6,737,000
Total changes........				+10,563,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....	586	580	-6
Full-time equivalent of overtime and holiday hours................	4	4	---
Average SES salary..................	$110,860	$113,299	+$2,439
Average GM/GS grade.................	10.0	10.0	---
Average GM/GS salary................	44,770	45,755	+985
Average salary, grades est. by act of July 1, 1944 (42 U.S.C. 207)....	54,365	55,561	+1,196
Average salary of ungraded positions.........................	0	0	---
Personnel compensation:			
Permanent positions................	$24,156,000	$25,108,000	+$952,000
Positions other than permanent.....	2,846,000	2,936,000	+90,000
Other personnel compensation.......	630,000	630,000	---
Special personal services payments.	548,000	548,000	---
Subtotal, personnel compensation.	28,180,000	29,222,000	+1,042,000
Personnel benefits..................	5,567,000	5,844,000	+277,000
Benefits for former personnel........	26,000	26,000	---
Travel and transportation of persons.	425,000	432,000	+7,000
Transportation of things............	98,000	100,000	+2,000
Communications, Utilities, and Miscellaneous Charges (23.3).......	1,650,000	1,679,000	+29,000
Printing and reproduction...........	1,236,000	1,258,000	+22,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Other services:			
Consulting Services	$467,000	$475,000	+$8,000
Other	33,419,000	40,433,000	+7,014,000
Purchases from Govt. Accts	14,549,000	14,836,000	+287,000
Operation of GOCOs	0	0	0
R&D Contracts	6,551,000	6,323,000	-228,000
Supplies and materials	523,000	532,000	+9,000
Equipment	8,727,000	8,884,000	+157,000
Grants, subsidies & contributions	24,330,000	26,267,000	+1,937,000
Total budget authority by object	125,748,000	136,311,000	+10,563,000

Note: Includes FTEs associated with HIV Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Library of Medicine

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	$24,156,000	$25,108,000	+$952,000
Other than Full-Time Permanent (11.3)	2,846,000	2,936,000	+90,000
Other Personnel Compensation (11.5)	630,000	630,000	---
Special personal services payments (11.8)	548,000	548,000	---
Total Personnel Compensation (11.9)	28,580,000	29,222,000	+1,042,000
Civilian Personnel Benefits (12.0)	5,567,000	5,844,000	+277,000
Benefits to Former Personnel (13.0)	26,000	26,000	---
Subtotal, Pay Costs	33,773,000	35,092,000	+1,319,000
Travel (21.0)	425,000	432,000	+7,000
Transportation of Things (22.0)	98,000	100,000	+2,000
Rental Payments to Others (23.2)	0	0	---
Communications, Utilities, and Miscellaneous Charges (23.3)	1,650,000	1,679,000	+29,000
Printing and Reproduction (24.0)	1,236,000	1,258,000	+22,000
Consulting Services (25.1)	467,000	475,000	+8,000
Other Services (25.2)	33,419,000	40,433,000	+7,014,000
Purchases from Govt. Accts (25.3)	14,549,000	14,836,000	+287,000
Operation of GOCOs (25.4)	0	0	---
Supplies and Materials (26.0)	523,000	532,000	+9,000
Total Administrative Costs	86,140,000	94,837,000	+8,697,000

NATIONAL INSTITUES OF HEALTH

National Library of Medicine

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation...	Title III, Part A Section 301	42 421	Indefinite		Indefinite	
National Library Medicine........	Title IV, Part D Section 465-478a	42 286	Such sums as necessary	$125,748,000	Such sums as necessary	$136,311,000
Total, Budget Authority........				$125,748,000		$136,311,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$56,408,000	$61,588,000	$62,088,000	$61,838,000
1988	64,399,000	71,465,000	70,399,000	67,910,000
1989	70,626,000	64,836,000 2/	70,626,000	73,731,000
1990	78,729,000	83,311,000	80,729,000	82,932,000 3/
1990 Sequester				-1,071,000
1991	89,916,000	80,725,000	94,416,000	91,408,000
1991 Sequester				-1,000
1992	100,554,000	99,565,000	100,549,000	99,088,000 4/
1993	107,561,000	103,923,000	103,923,000	103,639,000 5/
1994	133,349,000	118,481,000	120,481,000	118,019,000 6/
1995	135,330,000	123,274,000	127,274,000	125,748,000 7/
1996	136,354,000 7/			

1/ Reflects enacted supplementals, recissions and reappropriations.

2/ Excludes funds for Medical Library Assistance Act programs not considered.

3/ Excludes enacted administrative reduction of $379,000.

4/ Excludes enacted administrative reduction of $980,000.

5/ Excludes enacted administrative reduction of $1,385,000.

6/ Excludes rescission of $1,962,000.

7/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996. Excludes enacted administrative reductions of $271,000, $2,000 and $253,000.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Programs:												
Med'l. Lib. Assistance.		$15,071		$15,090		$15,685		$16,405		$16,855		$450
PHS 301		11,667		11,459		12,735		14,076		15,941		1,865
Total, Extramural		26,738		26,549		28,420		30,481		32,796		2,315
Intramural Programs												
Library Operations	364	37,799	360	38,574	345	45,154	337	48,265	336	49,225	-1	960
Lister Hill Center	90	14,236	86	14,142	81	19,488	82	24,143	80	31,028	-2	6,885
Biotechnology Center	38	6,459	37	10,156	32	9,277	34	9,714	33	9,905	-1	191
Toxicology Information.	39	4,722	38	4,936	37	4,865	36	5,045	35	5,144	-1	99
Total, Intramural	531	63,216	521	67,808	495	78,784	489	87,167	484	95,302	-5	8,135
Research Management and Support	107	7,926	104	8,038	101	7,797	97	8,100	96	8,213	-1	113
Total, Obligations	638	97,880	625	102,395	596	115,001	586	125,748	580	136,311	-6	10,563
Unobligated Balance Lapsing		151		117		236						
Total, Budget Authority	638	98,031	625	102,512	596	115,237	586	125,748	580	136,311	-6	10,563

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Library of Medicine

1994 Actual		1995 Appropriation		1996 Current Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
596	$115,237,000	586	$125,748,000	580	$136,311,000	-6	+$10,563,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Library of Medicine. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research."

Early in 1995, the one hundred thousandth user joined the National Library of Medicine's online network. The growth in users, and usage, is accelerating, at least in part because of the expanding reach of the Internet "information superhighway." So vital does NLM see the Internet for the health sciences, that it continues to support an "Internet connections" grant program and a variety of health care applications projects over the network.

The databases themselves continue their inexorable growth with 368,000 references, most with abstracts, added to MEDLINE in 1994. NLM's 50 databases contain almost 20 million records, including the latest in published medical findings and historical materials dating back to the eleventh century. In addition, the Library continues to expand the information it makes available via the Internet using such programs as Locator, telnet, file transfer protocol (ftp), Gopher, and Mosaic.

Further development of NLM information services are foreseen as a result of the Library's designation as a Reinvention Lab. Using the authority of the System Reinvention initiative, the Library is intensively reviewing how it can make use of new directions in software, hardware, and communications to provide more services to more people. Inherent in this effort is the central role of the Internet--as the route to deliver information and to facilitate user surveys and feedback that will refine the Library's offerings and services.

The NLM online network logged 6.9 million searches in FY 1994, 15 percent more than 1993 and the highest number ever recorded. A major reason is a significant increase in the number of users. The popularity of Grateful Med, combined with flat and fixed fee agreements with major educational institutions and medical professional associations, has spread the usage. Two other factors were also influential. In January 1994 the Library announced that its four databases containing HIV/AIDS information would henceforth be free to all users. Their use immediately doubled. Also, two new databases joined the NLM online family: HSTAR and HSTAT. These databases, containing information--including full text descriptions--about research related to health services--cost, access, and quality, including practice guidelines and technology assessment--are coordinated by NLM's National Information Center on Health Services Research and Health Care Technology. Another new database, retrievable only over the Internet, is *Images from the History of Medicine*, a collection of 60,000 historical images from NLM's History of Medicine Division.

Outreach to the health science community remains one of the Library's highest priorities. The information services offered, if they are to be of maximum benefit, need to be made widely known to physicians and other health professionals. A key to all of NLM's outreach efforts is the cooperation of the eight Regional Medical Libraries and the 4,100 members of the National Network of Libraries of Medicine. Some 50 major exhibits and hundreds of training sessions, workshops, and demonstrations, are conducted annually under the auspices of the Regional Medical Libraries. Following up on the announcement in January 1994 that NLM AIDS-related online databases would be provided without charge, the Library several months later announced that it would make small awards, up to $25,000, to local organizations to enable them to purchase computer and telecommunication equipment, and to gain training in the use of NLM's AIDS databases. NLM funded 19 such applications.

The High Performance Computing and Communications initiative is a major interagency program that includes 10 Federal agencies, including all the major science agencies. The Library is involved because high-performance computers and high-speed computer networks are key technologies for the future of biomedical science. Grand challenges in biomedicine, such as the analysis of the human genome, prediction of biological structure and function from genetic code, and rational drug design, require new and faster computers, advanced software, a national research and education computer network, and expanded training of scientists in the use of computer-based tools.

In FY 1994 the NLM funded 10 projects designed to help physicians practice better medicine by utilizing advanced computing and networking capabilities along the "information superhighway." These, and one funded in 1993, amount to an expenditure of $26 million over three years. The projects are funding HPCC healthcare applications such as testbed networks to share information resources; computerized patient records and medical images; telemedicine projects to provide consultation and medical care to patients in rural areas; and advanced computer simulations of human anatomy for training via "virtual surgery." The projects will also grapple with such issues as how to store, access, and transmit patient medical records while protecting their accuracy and privacy. The development of a system of computerized medical records is seen as crucial to applying the latest in computer and communications technology to medical care. In September 1994, the Library made five awards, totaling $1.5 million, to conduct research in areas related to developing electronic medical records systems. The Library is funding these projects jointly with the Agency for Health Care Policy and Research.

For the last three years, NLM has been supporting a project to create two 3-dimensional, computer-generated human beings--male and female. The Visible Man was introduced to the world at a meeting of radiologists in Chicago on November 28, 1994. The project,managed and funded by the NLM, was carried out by scientists at the University of Colorado Health Sciences Center in Denver. The Visible Man was created with digitized data compiled from the body of a 39-year who had willed his body to science. The donor body was imaged from head to toe using CT, MRI, and x-rays. It was then frozen and photographed in 1,800 millimeter-thin slices. The digital photographs were processed in an imaging computer system along with fiduciary marks and data acquired from radiologic studies. The resulting dataset is immense--15 gigabytes--that would take up to two weeks of uninterrupted Internet time to transmit in its entirety. This is the first time such detailed information about an entire human body has been compiled and there are many envisioned uses of the dataset. For example, it will be a powerful tool for introducing students to the human body, planning surgery, explaining physical processes to patients, and designing artificial joints and other fabricated body parts.

Another area of science that is tied intimately with HPCC is that of biotechnology. The National Center for Biotechnology Information, a research component of the NLM, creates and maintains systems for storing, analyzing, and retrieving information on molecular biology, biochemistry and genetics. Its GenBank database is regularly queried by remote users more than 10,000 times a day. Another research component, the Lister Hill National Center for Biomedical Communications, is responsible for coordinating the HPCC-related projects described earlier, conducts research in expert systems, medical linguistics, and other aspects of biomedical communications, and operates a hands-on facility called The Learning Center for Interactive Technology.

The President's appropriation request of $136,311,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Library of Medicine during the last five years has been as follows:

Year	Amount	FTEs
FY 1991	$90,888,000	621
FY 1992	98,031,000	638
FY 1993	102,512,000	625
FY 1994	115,237,000	596
FY 1995	125,748,000	586

Purpose and Method of Operation

To maintain information services in support of research, health care delivery, and education, the Library's programs are conducted and supported through the following activities: extramural programs, intramural programs, and research management and support. The primary goal of these activities is to ensure maximum application of biomedical knowledge and state-of-the-art health care improvements resulting from advances in biomedical research.

Overall Budget Policy

The FY 1996 budget request for the National Library of Medicine is $136,311,000, an increase of $10,563,000 over the comparable FY 1995 level of $125,748,000. The request includes support for 580 FTEs, a reduction of 6 FTEs below the FY 1995 level of 586 FTEs. The request continues to emphasize support for library operations including literature acquisition, management, dissemination, and preservation, and for grants in Integrated Advanced Information Management Systems, training, medical informatics, biotechnology and other research and development activities. The request includes a program increase of $8,000,000 for High Performance Computing and Communications. This level will permit NLM to institute new programs and enhance existing programs in connectivity, visualization, and database technology that may have profound impact on medical practice, research, and education. For extramural programs, the FY 1996 request is $32,796,000; an increase of $2,315,000 over the FY 1995 comparable level of $30,481,000. The request will support a total of 137 awards. For intramural programs, the FY 1996 request is $95,302,000; an increase of $8,210,000 over the FY 1995 comparable level of $87,092,000. For research management and support activities, the FY 1996 request is $8,213,000; an increase of $38,000 over the FY 1995 level.

National Library of Medicine

Extramural Activities

1996 Authorizing Legislation - Section 301, 465-467, and 469-477 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$28,419,000	$30,481,000	$32,796,000	+$2,315,000

The NLM's Extramural Programs (EP) Division provides a range of grants relating to the management, dissemination, and use of medical knowledge. Authorized by Public Health Service laws including the Medical Library Assistance Act (MLAA), these grants seek to improve biomedical communication and knowledge access and represent the only Federal programs focusing on information issues that concern the entire health community.

Funding for the NLM Extramural Programs during the last five years has been as follows:

FY 1991	$25,491,000
FY 1992	26,741,000
FY 1993	26,552,000
FY 1994	28,419,000
FY 1995	30,481,000

Rationale for Budget Request

The FY 1996 budget request for NLM's Extramural Programs is $32,796,000 which will support approximately 137 awards. This represents an increase of $2,315,000 and a decrease of four awards over the FY 1995 estimate of $30,481,000. With the FY 1996 extramural request these funds will provide support for the following activities: Medical Library Assistance, $16,855,000, an increase of $450,000 or 2.7 percent over the FY 1995 estimate of $16,405,000; PHS 301, $15,941,000, an increase of $1,865,000 or 13.2 percent over the FY 1995 estimate of $14,076,000.

Medical Library Assistance Programs

Integrated Academic Information Management System (IAIMS) Program--The IAIMS initiative is designed to create model computerized information systems to serve health professionals in complex academic health centers. IAIMS fosters integration such that from a desk top terminal, the user can gain rapid access to various institutional databases: e.g., patient records, laboratory tests and results, previous treatment protocols, pertinent bibliographic databases, remote files--such as a tumor registry in another state--administrative data, and clinical decision-making systems.

"One-stop information shopping" should be on all appropriate desk tops. IAIMS-like networking has become essential as our health delivery organizations gear up to take advantage of the extraordinary access to information which is being created by the government's National Information Infrastructure initiative.

NLM provides support to assist in the planning, development, and implementation of IAIMS. There are now seven institutions which have successfully competed for the implementation phase of this program.

To meet changing national needs, IAIMS was significantly revised in 1992 to shorten the development time, and to place greater emphasis on clinical elements such as quality control and outcome analysis, and on connections to national information networks. NLM plans to add two new operational grants by end of FY 1996.

Medical Library Resource Grants--Resource Grants assist health science libraries to improve information services to health personnel engaged in education, research and patient care. Present emphasis for the resource grants is on facilitating connection to national databases by networks for both health professionals and librarians. As the new technology penetrates the workplace, biomedical information will more and more be retrieved from a vast national library, composed of a myriad of local collections which are available to all through computers and telecommunications. This program offers two types of grants: Information Access Grants and Information Systems Grants.

The Information Access Grant is directed towards the libraries of small and medium-size hospitals and similar health-related institutions, and promotes access to information resources via new technologies. The Information Systems Grant, which also emphasizes computer and telecommunications technologies, is directed towards larger hospitals and academic health centers, and encourages networking, connectivity and systems integration. This program will be continued and expanded in 1996 due to the marked increase in applications now being received.

Research Grants in Medical Librarianship and Medical Information Science --NLM offers assistance for research and career development opportunities in Health Science Librarianship and Information Science. Investigations in this program area include evaluation of managerial and organization structure for improved information service, studies of how health information professionals perceive their information requirements, and how medical institutions can utilize new technologies for higher levels of information access. The program is expected to receive increased emphasis in FY 1996 in association with NLM's current planning panel on educational needs of the librarian of the future.

Training in Medical Informatics and Biotechnology Information--NLM is the prime supporter, nationally, of university programs which provide research training in medical informatics, and the related subfield which deals with biotechnology and molecular biology. Such programs are designed to train investigators who are well-equipped to address fundamental issues in the management of health knowledge. Trainees in this program will contribute to the growth of information sciences by analyzing special structures for managing this knowledge and will enable biomedicine to take advantage of the enormous capabilities of computer science for organizing, retrieving, and utilizing health knowledge.

To complement research training, NLM also funds a fellowship in applied informatics which is intended to fill an urgent national need for informatics professionals able to bring the results of research into practice. The fellowship will provide up to three years of training for those interested in learning some aspect of informatics which can then be applied to their primary discipline. IAIMS, newer library methods, computerized patient records, informatics aspects of radiotherapy, dentistry, and nursing, artificial intelligence programs, and medical education are among the areas which may be studied by such fellows.

The institutional training program reached its steady state in FY 1995 with about 120 fellows enrolled nationally. The fellowship in applied informatics has been particularly popular and will be significantly increased in FY 1996 because of the importance of such trained personnel in developing the new electronic information systems within our health institutions.

EP's Internet Connections program and the High Performance Computing and Communications (HPCC)--In consonance with the HPCC initiative, Extramural Programs plans to repeat the now annual program first offered in 1992 which provides funds to connect medical institutions to the Internet. A broad variety of health-related institutions including small community hospitals, are eligible to apply. The Internet, like the telephone system, will require a critical mass of users if it is to serve the biomedical community properly.

Outreach Initiative--NLM continues to extend its outreach activities to improve access by health professionals to NLM's information resources. The focus of these activities has been enhancing the National Network of Libraries of Medicine (NN/LM) and improving access by individual health professionals to NLM's information products and services, especially by persons presently unaffiliated with an institution and/or who are located in rural or other medically underserved settings. NLM's conducts special outreach programs to community-based AIDS organizations and to producers and users of health services research.

In FY 1996, NLM will award new competitive five-year contracts for Regional Medical Libraries in eight geographic regions to support the programs of the National Network of Libraries of Medicine. The focus will continue to be on bringing the best information services to health professionals in all parts of the country, with special outreach programs to unaffiliated, rural, and minority health professionals and emphasis on linking health professionals to the Internet and therefore to the global biomedical community.

In training, the newly established Fellowships in Applied Informatics have as one goal the training of professionals from underserved areas who can then return to their home institutions with the expertise needed to develop and implement modern biomedical information systems.

Almost all of the Information Access grants, and many of the Information Systems grants involve rural or inner city institutions. For FY 1996 NLM expects to place increased emphasis on the inner cities, which have so far received less support than rural areas.

Publications--The Publication program is small but vital because few alternate sources of support are available. This program provides small grants to scholars, primarily in the field of history of medicine and science, who seek partial support while preparing a manuscript for publication. In FY 1996 EP expects to broaden the program to include publications in CD-ROM and film in recognition of the increasingly important role of these alternates to print as sources of information.

Training of Health Sciences Librarians--NLM intends to continue in FY 1996 a grant program intended to foster development of ways and means for providing the nation with health sciences librarians appropriately sophisticated in the computer and telecommunication techniques which have revolutionized information storage and retrieval.

PHS 301 Programs

Medical Informatics Research--Through the medical informatics program, NLM supports work on fundamental knowledge issues. These concern the extraction, organization, retrieval, and utilization of knowledge, involving methodologies such as artificial intelligence, computer sciences, computational linguistics, medical decision sciences, cognitive psychology, and related information-oriented fields. Funds in FY 1996 will permit funding of six to ten new grants in this area. NLM expects to see particular emphasis on telemedicine, artificial intelligence programs to assist retrieval of stored information, and expert systems to assist medical decision making.

Biotechnology Information Research--In the area of biotechnology information, extramural research is supported to investigate effective methodologies of reorganizing and analyzing data relating to molecular control of life processes. Relevant problems include designing and managing databases, retrieving information from multiple factual databases, and pattern-matching algorithms for biological sequences. Scientific advances in molecular biology will depend in large part on successful resolution of knowledge and information issues. Grants in this area will increase. In addition, NLM expects to focus more support on vital national databases in protein structure and function which can serve as a national resource for investigators in this field. For FY 1996 NLM will continue to place emphasis on protein databases, genome sequence databases, and image databases which capture the physical structure of genetically-relevant molecules.

Computerized medical records--With support from HPCC funds, NLM, in cooperation with the Agency for Health Care Policy and Research, is supporting an important Cooperative Agreement granting program in the general area of the Electronic Medical Record System. NLM agrees with the widely-held belief that a nation-wide digital information base for documenting patient care is essential to health care reform, and modern health care management. A practical computerized patient record system must be developed if a national clinical database is to be achieved. The eight awards which have been made in this program have permitted creation of an interacting group which holds great promise for facilitating development of such key elements as a national machine-readable health sciences vocabulary, standards for interchange of information, and safeguards for privacy of clinical information. Because of the central importance of electronic health records to health care reform, this grant program has a high priority in FY 1996.

Educational Technology--the potential of computers and telecommunications for health education both for professionals and consumers is enormous but much remains to be done in the area of research and development. NLM has supported such work from time to time in its other programs and intends in FY 1996 to set aside some funds dedicated to this important area.

National Library of Medicine

Intramural Activities

1996 Authorizing Legislation - Section 301, 465-467, and 478 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
495	$78,828,000	489	$87,092,000	484	$95,302,000	-5	+$8,210,000

NLM's intramural activities are carried out by four major components: Library Operations acquires and preserves library materials pertinent to medicine; organizes these materials by cataloging and indexing; disseminates its authoritative bibliographic records online, in other machine-readable formats, and in publications; lends originals or copies of documents from NLM's comprehensive collection; provides reference and research assistance as a back-up to services available from the National Network of Libraries of Medicine; and develops and enhances information services in the field of health services research.

The Lister Hill National Center for Biomedical Communications explores the use of computer, communication, and audiovisual technologies for improving the organization, dissemination, and utilization of biomedical information. The National Center for Biotechnology Information performs basic and applied research using mathematical and computational approaches; collects and organizes molecular sequences data; develops software tools for analyzing and accessing data; and distributes data through high-speed network-based systems and other electronic media.

The Specialized Information Services (SIS) manages the Toxicology Information Program (TIP) and develops computerized databases in pharmacology, toxicology, and environmental sciences. They include data related to long-term, low-level exposure to hazardous substances, and on the health effects induced by chemical carcinogenesis, teratogenesis, and mutagenesis. TIP is one of the Nation's most important sources of information for emergency response to toxic chemical spills and the release of other health and environmental or occupational hazards.

Funding for the Intramural Programs during the last five years has been as follows:

Year	Amount	FTE's
FY 1991	$57,954,000	515
FY 1992	63,326,000	531
FY 1993	67,865,000	521
FY 1994	78,828,000	495
FY 1995	87,092,000	489

Rationale for the Budget Request

The FY 1996 budget request for Intramural Programs is $95,302,000. This is an increase of $8,210,000 over the FY 1995 comparable level of $87,092,000 and will provide increased funding for the high performance computing and communications initiative.

Library Operations

NLM's basic mission is to collect, organize, and provide access to information in the world's biomedical literature in support of the progress of medicine and the improvement of public health. Library Operations acquires and preserves the biomedical literature; organizes this literature through authoritative cataloging and indexing, using the biomedical subject thesaurus it develops and maintains; disseminates NLM bibliographic records online, in machine-readable formats, and in publications; lends or copies documents in the NLM collection as a back-up to document delivery service provided by other U.S. biomedical libraries; provides reference and research assistance to health professionals; and maintains an active program of scholarship in the history of medicine. Library Operations also directs the National Network of Libraries of Medicine or NN/LM to enhance the general level of biomedical information service available throughout the United States. In FY 1996, NLM's System Reinvention will improve automated support for many of these essential programs and services.

Acquisition--NLM is the largest biomedical library in the world, with a collection of 4.9 million items including books, journal volumes, theses, pamphlets, audiovisuals, computer software, microforms, pictures, and manuscripts. To maintain and enhance this comprehensive collection, in FY 1996 the Library will continue to purchase the world's biomedical literature in an increasing variety of formats. The cost of biomedical literature invariably increases at a rate that far exceeds general inflation and is particularly vulnerable to fluctuations in currency exchange rates. In FY 1996, NLM expects to install commercial integrated library system software as a basis for more efficient handling of library materials from the point they are ordered through subsequent processing and use.

Collection Preservation and Maintenance--NLM works to ensure the long-term availability of the scholarly record of biomedicine by preserving endangered items in its collection and promoting the use of more permanent materials in new biomedical publications. In FY 1996, the Library will use contract assistance to bind more than 25,000 volumes, microfilm about 5,000 brittle books and journal volumes, and conserve several hundred rare or unique items from its rare book, manuscript, picture, and audiovisual collections.

Creation of Bibliographic Data--One of NLM's most important activities is the creation of the authoritative records that describe available biomedical information sources, including journal articles, books, and electronic databases. These records provide an essential foundation for the Library's online retrieval, reference, and document delivery services. In FY 1996, NLM expects to describe the contents of about 400,000 articles; 22,000 books, serials, audiovisuals, and computer software packages; and hundreds of biomedical databases available on the Internet. The Library will obtain assistance for this work from contracts, interagency agreements, and

International MEDLARS Centers. As part of the NLM System Reinvention, the several systems used to create, store, and update NLM's authoritative bibliographic data will be replaced by a more flexible, efficient, and integrated file building system that eliminates redundant data creation.

Dissemination of Bibliographic Data--NLM's authoritative bibliographic data are distributed online, in various machine-readable formats, and in a diminishing set of printed publications. In FY 1996, NLM will continue to emphasize the electronic dissemination of its data via the Internet and begin to phase out some printed publications.

NLM has more than 100,000 online users and this number is expected to continue to increase at the rate of at least 15-25 percent per year, due to a combination of outreach efforts, convenient pricing arrangements, and improvements in the range of information offered and in online access mechanisms such as Grateful Med. In FY 1996, NLM will consolidate some of its databases to provide easier access for users while also reducing database production and maintenance overhead. At the same time the amount of information available to users will increase, especially in the areas of health services research, ongoing clinical trials, full-text clinical practice guidelines, and full-text health education materials produced by NIH Institutes. NLM will also provide online access to an increasing amount of its post-World War II indexing data, important due to the resurgence of tuberculosis, the investigation of early human radiation experiments, etc. In FY 1996, many online users will access NLM's databases via a new Internet-based version of Grateful Med, another product of NLM's System Reinvention. This program will use the UMLS Knowledge Sources to help convert the user's words into appropriate search terms and to identify the databases likely to contain information relevant to particular questions.

Reference Services and Document Delivery--NLM provides reference service and document delivery as a national back-up to services available from the more than 4,100 members of the National Network of Libraries of Medicine, as well as serving onsite users of NLM's collection. The Library expects to respond to more than 65,000 reference requests and to process at least 550,000 document requests in FY 1996. By that time the number of health sciences libraries using DOCLINE, NLM's automated request and routing system, is likely to be more than 3,000 and the system should be handling an annual volume of more than 3 million document requests, including many automatically referred by individual health professionals who use the Loansome Doc feature of Grateful Med. An increasing percentage of these requests will be filled by transmission of electronic page images via the Internet. NLM will continue to work through its National Network of Libraries of Medicine program to increase the number of health sciences libraries and health professionals with high speed connections to the Internet that allow the most efficient use of many of the Library's services.

Health Services Research--NLM's National Information Center on Health Services Research and Health Care Technology coordinates Library-wide efforts to improve access to information needed by health services researchers and to disseminate the results of health services research, including clinical practice guidelines and technology assessments, to health care professionals, administrators, policy makers, and public health officials. In 1996, the Library will continue to index an increasing amount of health services research literature, including technical reports and government publications, and to enhance or build databases of full-text clinical practice guidelines, health services research-in-progress, data sets useful in the conduct of health services research, and tested survey instruments. In collaboration with the National Network of Libraries of Medicine, NLM will focus special outreach efforts on public health officials and other groups that need access to the results of health services research and will continue to train the country's health sciences librarians to respond to health services research information needs and to contribute to local health services research projects.

Better computer-based patient record systems will allow extensive health services research data to be produced as a by-product of current health care. To foster the development of such systems, NLM will continue to collaborate with the Agency for Health Care Policy and Research to promote the development of a standard clinical vocabulary for use in patient records; to apply NLM's UMLS Knowledge Sources to the problem of linking individual patient records to relevant information in practice guidelines, expert systems, and bibliographic and factual databases such as those created by NLM; and to develop workable strategies for abstracting useful health services research data from patient record from patient record systems while safeguarding patient privacy.

Lister Hill National Center for Biomedical Communications

The Lister Hill National Center for Biomedical Communications (LHNCBC), a research and development division of the National Library of Medicine, supports the Library and the health information user community by investigating how to apply advanced computer and communications technologies. Center projects develop and implement new computer and information science methods to organize and provide access to the enormous quantity of knowledge in the life sciences. This knowledge includes the text of journal articles, monographs, digital images, facts from databases, and the representation of medical problem-solving and other expertise.

Research projects conducted and supported by the Center included applications of computer technology as varied as the display and analysis of three dimensional electronic images of human anatomy for more accurate instruction of health professions students and the development of natural language understanding programs to enable computers to "read" and translate biomedical literature. LHNCBC will initiate or extend several major program efforts in FY 1996:

Three Dimensional Anatomic Imaging. The Center will continue work on its "Visible Human" project to construct a digital library representing complete human beings at millimeter level resolution. The long term goal of the project is to produce a system allowing one to search for pictures using words and concepts, and for words and concepts using pictures. Currently LHNCBC is beginning to distribute the Visible Human data in an electronic publication media, and over the Internet; and continuing development for a two dimensional database system which underpins the 3-D display graphics. In fiscal year 1996, the Center will extend the image data distribution and continue testing of the first models for the two dimensional database.

Digital Radiology Images. LHNCBC will complete and test a system called DXPnet (Diagnostic X-ray Prototype Network) which can store and transmit radiology images over the National Research and Education Network. Networking will permit physicians to examine x-rays housed in a geographically separated locations and increase collaboration between similarly separated investigators.

Collaborative Research. In FY 1996 the LHNCBC will continue supporting collaborative research in biomedical applications of computing and digital communications. Part of the overall NIH HPCC effort, this research was initiated in FY 1993.

The 12 projects, scattered across the nation, fund health care applications such as testbed networks to share information resources, computerized patient records, and medical images; telemedicine projects to provide consultation and medical care to patients in rural areas; and advanced computer simulations of human anatomy for training via "virtual surgery." These projects were the first awards in health care to be made under the High Performance Computing and Communications Program. The published results and applications demonstrated will increase the expertise available within the health care community. Additional research is being funded through grants or cooperative agreements. LHNCBC will also continue to investigate advanced models for accessing and delivering to users, medical information in many forms from existing and developing data bases of words, pictures, sounds and laboratory results.

DocView (Document Delivery of Internet). The DocView program represents a possible model for paperless electronic publication. When completed it will allow a remote user to retrieve images of a document over the Internet, read pages, electronically "bookmark" selected pages, magnify, modify, cut and paste images, and retain selected material in electronic or print formats.

Unified Medical Language System. NLM's UMLS Project develops, tests, and implements Knowledge Sources and software that help health professionals and researchers to overcome the barriers to effective information retrieval caused by the differences in the vocabularies used in different types of information sources and by the huge number of disparate databases and systems that may have information relevant to a particular question. Due to NLM's System Reinvention project, in 1996 many of NLM's online users will be using a new Internet version of Grateful Med that uses the UMLS Knowledge Sources and associated programs to provide assistance in preparing effective searches and selecting the databases most likely to be relevant to particular questions. A greatly expanded UMLS Information Sources Map will contain descriptions of biomedical information sources available via the National Information Infrastructure. This map will be maintained and updated via the Internet with assistance from the producers of the information sources and members of the National Network of Libraries of Medicine. The content of the UMLS Metathesaurus will continue to expand rapidly to support increasing use as a source of "standard" vocabulary for computer-based patient record systems and as a tool for linking sources of information useful in health care decisions such as practice guidelines, MEDLINE and expert systems, to machine-readable patient records.

National Center for Biotechnology Information

The National Center for Biotechnology Information (NCBI) is responsible for managing and distributing the rapidly growing body of information in the field of molecular biology, particularly genetic sequence information. Progress in the field of molecular biology and commercial applications in biotechnology depend on the availability of comprehensive, accurate, and up-to-date sequence databases.

NCBI serves the biology and biotechnology community by: (1) performing basic and applied research in biology using mathematical and computational approaches; (2) collecting, organizing, and distributing information about molecular sequences in the NIH GenBank database; (3) developing new software tools for researchers to analyze sequence data; and (4) providing high-performance public access search systems to retrieve GenBank and related bibliographic data.

The major database responsibility of the NCBI is the NIH database of sequence data, GenBank. GenBank is the world's foremost collection of DNA sequence data, now numbering over 230,000 different sequences and over 230 million base pairs of data from over 5,000 different species. Due to the rapid pace in sequencing technology and the proliferation of laboratories involved in sequencing, NCBI must cope with the database's exponential rate of growth: a doubling in size every 20 months. As a data resource it is used by every molecular biology laboratory throughout the world involved in gene sequencing to determine whether a sequence is new and what its function may be.

In FY 1996, the GenBank database is expected add some 300,000 sequences from human CDNA clones. These sequences will be produced at the Sequencing Center at Washington University in Missouri as the result of an agreement between the Center and the Merck pharmaceutical company to create a comprehensive, publicly available database of human expressed sequence tags (ESTs). These sequences are an extremely important resource for researchers to identify and characterize genes responsible for human disease. The agreement between Merck and Washington University is unprecedented in establishing a project with a specific goal of open, non-propriety access to information. NCBI will assume the critical role of ensuring that the sequences, which will be generated at the rate of 6,000 to 8,000 per week, are properly entered into the database and made immediately available to the public. The dbest (Database of Expressed Sequence Tags), which NCBI created two years ago in order to accommodate the detailed information specific to CDNAS that was not carried by GenBank, will initially accept the data and pass through the appropriate sequence information to GenBank, which will then propagate the new data through daily updates over the network and to the other international sequence databases.

Along with growth and comprehensiveness, accuracy of data is crucial for the utility of a scientific database. NCBI will continue its commitment to ensure that the quality and the accuracy of GenBank is of the highest caliber possible. NCBI has started a GenBank Fellows training program in which, for the first year, six postdoctoral fellows have been chosen from over 200 applicants. The fellows' primary responsibility is to improve the quality and annotation of GenBank entries and in the process receive training in bioinformatics. Already projects have begun to screen out contaminating vector sequences, to improve the uniformity of taxonomic usage, and to link related information, such as three-dimensional macromolecular structures.

In addition to the 300,000 EST sequences, the current rate of growth would predict that at least another 80,000 sequences will be added in FY 1996. In order to facilitate the input of sequences from individual laboratories and researchers, NCBI is developing new data submission software that will enable a researcher to use familiar Internet tools, such as the World Wide Web, to prepare a sequence for GenBank. Not only will the process become more convenient for users, but the interactive nature of submitting sequence data will permit a series of automated checks to be run and feedback from the author to be obtained before the sequence is formally submitted to GenBank. Quality will improve, but the interactive nature of the submission will greatly improve the timeliness of entries.

As part of ongoing programs to link and integrate all available sequence information, NCBI will be adding data from protein structural databases, such as the Protein Data Base (PDB). The Molecular Modeling Database (MMDB) is being constructed at NCBI to present 3-D structure information in a form convenient for researchers in the area of molecular modeling and rational drug design. With MMDB integrated in other NCBI databases, users will be able to identify proteins which appear to be related by combinations of strong sequence and/or structural similarity.

NCBI is a major center in the High Performance Computing and Communications initiative. Over 25,000 different sites have used NCBI network services over the past year. Each day over 10,000 queries are handled by NCBI computers including thousands of queries which involve computer-intensive comparisons of a single sequence against the entire database. New software and databases are being designed which take advantage of clusters of scaleable, parallel servers which are used to keep search times under a few seconds even for very extensive searches. Through its network and CDROM Entrez systems, NCBI provides researchers with both sequence data as well as bibliographic information from Medline which is linkable to sequences and the proteins they encode. NCBI is recognized as the major international site for comprehensive and fast sequence database searching and through incremental hardware upgrades to the scaleable supercomputers, will be able to handle the increasing size of the database and the increase in the number of users.

NCBI will continue to work with other Federal agencies such as the Department of Agriculture and the U.S. Patent and Trademark Office (USPTO) to ensure that sequence data, respectively, from the Plant Genome Project, and in issued patents is included. NCBI collaborates closely with data sources in Europe, European Molecular Biology Laboratory, and in Japan, National Institute of Genetics, to maintain international coverage of gene sequence information.

Finally, NCBI will continue to strengthen its extensive intramural research program in computational molecular biology and play a key role in assisting gene sequencing groups in the analysis and identification of function of newly sequenced DNA and in protein structure prediction. Senior NCBI scientists work closely with the NIH intramural research program in human genome research as well as with programs at academic institutions where NCBI expertise in sequence analysis has been instrumental in the discovery and analysis of human disease genes.

Toxicology and Environmental Health Information Program (TEHIP)

The Division of Specialized Information Services (SIS) - manages a national Toxicology and Environmental Health Information Program and develops computerized databases in the fields of chemistry, pharmacology, and toxicology, as well as the environmental and the health sciences. All SIS databases are now available on the INTERNET, a worldwide matrix of interconnected networks used by millions of computer users. In FY 1996, NLM will continue supporting and expanding these services and maintain the same level of collaborative relationships with other Federal agencies and the private sector. Private sector vendors license these databases for Online or CD-ROM distribution, thus increasing access to this national resource of chemical, toxicological, and health information.

The Toxicology Data Network (TOXNET) and its data banks constitute one of the world's most comprehensive sources of information on the health and environmental effects of hazardous substances. This computer system will continue to offer the following array of services: The Hazardous Substance Data Bank containing data on about 4,500 chemicals whose "exposure potential" is of concern. These data are relevant to human and animal toxicity, biomedical effects, safety and handling, human exposure, environmental fate, and other related areas. The Toxic Chemical Release Inventory (TRI) series of files, compiled and maintained by the EPA, are made publicly available on TOXNET. TRI contains data collected annually from industry on the amounts of some 330 specified chemicals released to the environment or transferred to waste sites. In 1996, the data collected will include the pollution prevention activities of the reporting facilities.

Additional TOXNET data banks made available through collaborative agreements with other agencies, include: the Chemical Carcinogenesis Research Information System (CCRIS), a data bank containing published test results from carcinogenicity, genotoxicity, and tumor promotion studies; the Integrated Risk Information System (IRIS), which contains health risk and regulatory information for both carcinogens and non-carcinogens; the GENE-TOX file, which contains data on genetic toxicology; the Registry of Toxic Effects of Chemical Substances (RTECS); Developmental and Reproductive Toxicology (DART), a bibliographic database concerned with agents that cause birth defects and infertility, as well as the effects of neonatal and childhood exposure, and the Environmental Mutagen Information Center (EMIC) database which contains citations to the literature on agents that have been tested for genotoxic activity.

SIS will also continue to support and enhance CHEMLINE (Chemical Dictionary Online) which assists the user in searching NLM's bibliographic and data files for chemical, toxicological, and medical information. The file contains about 1,260,000 records. ChemID (Chemical Identification File) is an Online directory which contains 268,000 records and provides a link to selected lists of chemicals maintained by key regulatory and scientific organizations. Data from the European Inventory of Existing Chemical Substances (EINECS), are also available. TOXLINE and TOXLIT are "toxicology" bibliographic retrieval services, which contain over 3,962,000 records.

The Directory of Information Resources Online (DIRLINE), is NLM's directory of 17,592 health and biomedical information and service providers. These resources include voluntary organizations, NIH-supported scientific resources available for use by other biomedical researchers, self-help organizations, poison control centers, and Federal health information clearinghouses. The database has recently been expanded to include electronic resources such as databases and bulletin board systems covering all aspects of health. A subfile on biotechnology information resources, containing over 2,000 records and describing databases and other information services, organizations, collections and repositories, publications, and sanctioned nomenclature committees, has also been added. This database is available free-of-charge.

The Toxicology and Environmental Health Information Program continues to strengthen the capacity of Historically Black Colleges and Universities to search and utilize the information resources which it has developed. NLM remains committed to providing such services to health professionals in these schools.

National Library of Medicine

Research Management and Support

1996 Authorizing Legislation - Section 301, 465-467 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
101	$7,990,000	97	$8,175,000	96	$8,213,000	-1	+$38,000

Research Management and Support funds the salaries and expenses of the staff who provide for overall administration and direction of the National Library of Medicine programs, including the extramural grant and contract programs. Among functions carried out in this activity are execution of basic administrative services; contracts processing and management; grants management and the scientific direction of NLM's extramural programs, financial and personnel management; coordination of equal employment opportunity activities; direction of NLM's international programs; public inquiries and management of the Library's publications; and operations research. NLM's planning and evaluation activities are also provided for in this activity.

Funding for Research Management and Support during the last five years has been as follows:

Year	Amount	FTE's
FY 1991	$7,443,000	106
FY 1992	7,964,000	107
FY 1993	8,095,000	104
FY 1994	7,990,000	101
FY 1995	8,175,000	97

Rationale for Budget Request

The FY 1996 budget request for Research Management and Support is $8,213,000 and represents an increase of $38,000 above the FY 1995 appropriation of $8,175,000. Through this activity, NLM will continue to provide efficient and effective administrative support and management, and scientific direction for its programs.

96

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Request
Library Operations.............	345	337	336
Lister Hill Center.............	81	82	80
Biotechnology Center...........	32	34	33
Toxicology Information.........	37	36	35
Research Management and Support.	101	97	96
Total........................	596	586	580

Average GS/GM Grade

1991	GS-10.0
1992	GS-10.0
1993	GS-10.0
1994	GS-10.0
1995	GS-10.0
1996	GS-10.0

Note: Includes FTEs associated with HIV Research Activities. These FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive level I..........			
Executive level II..........			
Executive level III.........			
Executive level IV..........			
Executive level V...........			
Subtotal.............	0	0	0
Total - Exec. Lev. Sal......			
ES-6........................	0	0	0
ES-5........................	1	1	1
ES-4........................	3	3	3
ES-3........................	1	1	1
ES-2........................	0	0	0
ES-1........................	2	2	2
Subtotal.............	7	7	7
Total - ES Salary....	$721,300	$744,526	$760,905
GS/GM-15....................	28	24	24
GS/GM-14....................	41	37	37
GS/GM-13....................	82	82	82
GS-12.......................	156	155	154
GS-11.......................	34	34	33
GS-10.......................	0	0	0
GS-9........................	19	19	19
GS-8........................	25	25	24
GS-7........................	75	74	73
GS-6........................	42	42	41
GS-5........................	17	17	17
GS-4........................	41	41	40
GS-3........................	10	10	10
GS-2........................	5	5	5
GS-1........................	0	0	0
Subtotal.............	575	565	559

Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Suregon General	0	0	0
Director Grade	1	1	1
Senior Grade	1	1	1
Full Grade	1	1	1
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	3	3	3
Ungraded	18	18	18
Total permanent positions	603	593	587
Total full-time equivalent (FTE) employment, end of year.....	596	586	580
Average ES level............	ES-3	ES-3	ES-3
Average ES salary...........	$107,402	$110,860	$113,299
Average GS/GM grade.........	GS-10	GS-10	GS-10
Average GS/GM salary........	$43,645	$44,770	$45,755

THURSDAY, MARCH 23, 1995.

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

WITNESSES

DR. FRANCIS S. COLLINS, DIRECTOR
DR. ELKE JORDAN, DEPUTY DIRECTOR
JAMES C. VENNETTI, EXECUTIVE OFFICER
ERIN S. BURGESS, BUDGET OFFICER
DR. HAROLD E. VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. The subcommittee will come to order.

We continue our hearings on the National Institutes of Health, and welcome this morning Dr. Francis Collins of the National Center for Human Genome Research. We're delighted to see you, Dr. Collins. If you would, introduce the people at the table with you and proceed.

INTRODUCTION OF WITNESSES

Dr. COLLINS. Thank you very much, Mr. Porter.

Beginning at my far left, Mr. Jim Vennetti is the Executive Officer of the National Center for Human Genome Research; Ms. Erin Burgess is our Budget Officer. On my right, Dr. Elke Jordan, the Deputy Director; and you're familiar with Dr. Varmus, I presume, and with Mr. Dennis Williams from the Department.

OPENING REMARKS

Mr. Chairman, the noted architect Daniel Burnham, from your hometown of Chicago, penned the following memorable words, which I've become quite fond of: "Make no little plans; they have no magic to stir men's blood and probably themselves will not be realized. Make big plans, aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, but long after we are gone will be a living thing, asserting itself with evergrowing insistency."

Mr. Burnham was speaking of buildings, of course, and the blueprints for them. But his inspiring words apply remarkably well to the Human Genome Project. This ambitious and profoundly significant scientific undertaking aims to determine the complete maps and sequence of all of the human DNA by the year 2005. Surely, this will be a noble, logical diagram which, once recorded, will never die.

As this historic effort to read our own blueprint approaches its fifth birthday, I'm happy again to report that the project is running ahead of schedule and under budget. That this has been possible is a testimony to the wisdom of the original planners of the project, to the hundreds of scientists now dedicated to achieving its goals, and, I might say, to this committee, who had the courage and foresight to initiate funding for this project even when many around you were saying it couldn't be done.

I could spend my brief time with you enumerating the remarkable achievements in genetic and physical mapping over the past year, the accomplishments of the new intramural program, and the exciting opportunities that now exist for DNA sequencing in the coming year. But I thought instead that I would put these achievements in context by telling you about a woman named Beth, whose medical history is illustrative of the dramatic advances being made possible by the Human Genome Project.

You have in front of you a new color brochure which is entitled "The Human Genome Project: From Maps to Medicine," which was just published yesterday, and which I hope you will find enlightening. If you look on the inside back cover of this brochure, you will read about Beth in Case One.

Her story begins five years ago. At age 37, Beth faced an uncertain future. Her paternal grandmother, father and two brothers had been diagnosed with colon cancer. Her physician told her that with this family history, she was also at high risk, and recommended she begin annual colonoscopy to try to detect any incipient cancers while they were still small and treatable.

She agreed, but as you can imagine, felt constantly uneasy about this "family curse," as she refers to it. You might also be at risk for cancer of the uterus, her physician told her. But we are not as good at detecting uterine cancer early. Beth contemplated a hysterectomy, and worried about her children and what their risks might be.

Beth's family has hereditary non-polyposis colon cancer, or HNPCC. She is at 50 percent risk of inheriting a gene which has a misspelling in it from her father. And if she has inherited that misspelling, her chances of getting colon cancer are about 80 percent. Approximately 1 million people in the U.S. are in this same category.

Ten years ago, most people would have considered it ridiculous that we could actually identify the genes responsible for this condition called HNPCC. With about 100,000 genes in the genome, the idea of finding the right one or two or three—a process called positional cloning—seemed a truly impossible task. But the Human Genome Project has changed all of that. Genetic maps now make it possible to pinpoint, on the right chromosome, the location of disease genes for conditions like HNPCC.

In fact, last October, an international group of scientists led by our Genome Science and Techology Center at the University of Iowa, published a map of genetic markers. This map consists of about 6,000 bits of DNA scattered over all the human chromosomes, so that you can now very precisely map genes for conditions like HNPCC. I might say this is one of the first dramatic completions of one of the major initial goals of the Human Genome Project, and it has been done more than a year ahead of schedule. The map is about four times better than what we originally thought could be achieved.

Using that kind of approach, the HNPCC gene found in Beth's family was mapped to a small region of chromosome 2. But of course, you not only want to know the general region, you want the gene itself. Now, here is where new technologies developed to deal with large stretches of DNA come into play. One of those, microdissection of human chromosomes, which you may have seen when you visited the NIH, and is also depicted in this brochure, was used in this search.

Another technique, called physical mapping, where you construct a collection of cloned DNA fragments that cover all regions of all human chromosomes, is also being supported by the Human Genome Project. We are probably within a year and a half of having 90 percent of the human genome contained in overlapping physical clones. Already, three chromosomes are complete and five others are very close.

[CLERK'S NOTE.—Subsequent to the hearing, number of chromosomes completed was corrected to four and number near completion was corrected to four.]

Those efforts led to, over the past year, the identification of a total of four different genes that play a role in HNPCC. This discovery was made by investigators at Johns Hopkins University, at Dana-Farber Cancer Institute, at the University of Vermont, here in the intramural program of NCHGR, and the University of Helsinki in Finland. The research conducted in the U.S. was supported by the National Cancer Institute as well as the National Center for Human Genome Research.

All of these HNPCC genes, if you look at their sequence, turn out to be involved in spell-checking of DNA, which was an interesting revelation. Cancer is a result of mutations, and mutations are after all misspellings in DNA. If there is a problem with the system that corrects errors each time DNA is copied, then the risk of cancer is going to be predictably higher. And that's exactly the case for HNPCC.

We knew that this mechanism was correct almost immediately because of work that's been done in yeast and bacteria, on this same family of genes. This points out the extreme importance to the Human Genome Project of studying not only Homo sapiens, but other model organisms, which the genome project is heavily invested in.

Let's get back to Beth. Sequencing of DNA from her brothers and her father showed a subtle change in one of the HNPCC genes. In her two brothers and father there was a G in one place where there should been a C. Of course now, she is wondering, "Should I find out whether I too have inherited this."

These are complicated questions. Issues surrounding genetic testing of this sort are complex and challenging. Through the Ethical, Legal and Social Implications component—so-called ELSI—of the Human Genome Project, NCHGR has been investing more than 5 percent of its budget on these issues over the course of the last four or five years. A number of advances and recommendations have been made about these issues through ELSI research and the policy deliberations undertaken by the ELSI Working Group.

ELSI goals, at the present time, include ethical issues surrounding genetic research, particularly informed consent. Another issue is the appropriate timing of introduction of a new test, like colon cancer testing, into clinical practice. We have a Genetic Testing Task Force which will have its first meeting in two weeks, and which will be looking intensively at those issues, and also at the regulation of genetic testing to be sure that quality control is attended to.

Privacy and the fair use of genetic information are another set of ELSI issues. Several states have legislation in this area, and the Federal Government has begun to turn its attention to these issues. We strongly encourage these developments particularly in the area of health insurance reform.

In order to investigate some of these ELSI issues, a series of pilot projects has been funded by NCHGR, the National Cancer Institute, the National Institute of Nursing Research and the National Institute of Mental Health. Eleven projects are now underway to identify individuals in cancer families, offer them DNA testing and counsel them about the results. This applies not only to colon cancer, but also to the breast cancer gene, BRCA1, and ovarian cancer.

So Beth has enrolled in one of these pilot projects and has gone through the testing. The outcome, happily for her, is that she turns out not to have the mutation. Therefore, the colonoscopy that she has been going through yearly for the last five years turns out to be unnecessary. The hysterectomy that she was contemplating is also unnecessary. Her children, who she was quite frightened about, are in the clear. She didn't inherit the mutation, therefore she can not pass it on. This story makes the point that genetic testing not only identifies people at high risk, but it also identifies people who thought they were at high risk and turn out not to be at high risk.

This is a paradigm for other diseases. A future of individualized preventive medicine becomes possible when you imagine that DNA testing may be able to identify each person's individual risks, particularly for conditions where we know that early diagnosis can be lifesaving.

There is an assumption this new technology will increase costs. I would argue that in this particular instance, that's not the case. Working with economists at the NCI, we have done a thorough study of the cost benefits of doing HNPCC DNA testing in individuals with a family history of colon cancer.

In fact, it appears that this kind of testing, when coupled with colonoscopy on individuals found to be at high risk—so that their tumors can be detected while they're still small and benign, thereby sparing the cost of treating them for metastatic disease later on—is cost effective, probably more so in fact than mammography. That is an exciting outcome, and one which we're quite excited about propagating.

I used this scenario of Beth's story to make the case for the importance of the various components of the Human Genome Project, while they are wonderful basic science, and they are, and they are good for the American economy, and they certainly are, they have profound implications for the future of medicine.

I would like to close with an appeal to this committee to maintain the vision of a bright and healthy future for our nation based on advances made in biomedical research. Here I'm speaking not only about the Human Genome Project, but about the whole panoply of research supported by the NIH. Research! America recently conducted a survey indicating that 91 percent of Americans believe this nation should spend more on medical research to better diagnose, prevent, and treat disease. This is, after all, the mission of the NIH.

Yet within this past week, we have heard of proposals which would effectively cut the NIH budget by 29 percent over the next five years. That would be a devastating blow, particularly coming at a time of such enormous scientific opportunity. Biomedical research is a spectacularly good investment, representing a tiny fraction of our health care costs. For example, in the time from right now, 10:10 a.m., until the committee recesses for lunch, this nation will have spent more money on health care than we will spend in the entire year on the Human Genome Project.

I fully understand the mandate this Congress has to be fiscally responsible. But this research will pay for itself many times over. I understand that we must not mortgage our children's future to ever-increasing budget deficits. But how will we explain to our parents, our brothers, our sisters, our spouses, and our children, that we lost our will to heal their diseases? What kind of mortgaged future is that?

Surely we are not just interested in their financial health, but also their physical health.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1996 is $166,678,000. I will be happy to answer your questions.

Mr. PORTER. Can I take you with me when I go visit the Budget Committee people? [Laughter.]

Dr. COLLINS. Delighted.

[The prepared statement and biography of Dr. Francis Collins follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Human Genome Research

Mr. Chairman, fiscal year 1996 marks the end of the first five years and the beginning of a new era in the Human Genome Project. When the project began in 1990, we had established an ambitious plan to guide the research through these first five years. It is very rewarding to report to you today that we have indeed met or exceeded most of those goals--some ahead of time and all under budget. The benefits of that success are already widely apparent, as significant discoveries of the genetic basis of a vast number of genetic diseases--from polycystic kidney disease and spinomuscular atrophy to breast cancer, colon cancer, and diabetes--are happening at a staggering pace.

The new age of molecular medicine based on these gene discoveries holds promise for a wide range of customized, cost-effective approaches to health care of the individual, from early diagnosis, to treatments, and cures. Among the first of these technologies to emerge, genetic testing provides the opportunity to identify individuals at risk for inherited disease well before they become ill. This is likely to be most true for families prone to certain cancers, such as hereditary colon cancer. Genetic testing members of families in which colon cancer is prevalent, for example, can identify individuals who are at high-risk at a time when prevention or early intervention strategies are most effective and least costly. Genetic tests can also identify family members who are not at increased risk, sparing them from annual colonscopies.

This past year, an international consortium headed by the Genome Science and Technology Center in Iowa published a genetic map containing almost 6,000 markers spaced less than 1 million bases apart. The density of markers on this map is four to six fold greater than the goals set in 1990 called for, and it was accomplished more than a year ahead of schedule. In another major project to generate a genetic map of the mouse, technology development moved so quickly that a high-resolution genetic map of the mouse genome was completed in just two years. Because the mouse and human genomes are strikingly similar, genes identified and cloned from mouse DNA can provide crucial clues to the location and function of human genes. NCHGR is now helping to coordinate an initiative with other NIH Institutes, particularly NHLBI, to develop a high-resolution genetic map of the rat, another important model organism.

Physical mapping provides cloned sets of overlapping pieces of DNA that span a region of a chromosome, or even a whole chromosome, and serve as a resource for investigators who wish to isolate a gene they have located in a particular region on a chromosome. The first five-year goal of developing overlapping sets of cloned DNA that each spanned at least 2 million bases of DNA has been easily exceeded. Today, these so-called "contigs" are many times longer than the plan called for--ranging from 20 to 50 million DNA bases in length. In the near future, we expect over 90 percent of the human genome to be covered by overlapping DNA clone sets, each of which is at least 10 million bases long. Nearly complete cloned DNA sets have been developed for chromosomes 3, 4, 7, 11, and X. Recently, investigators at the Genome Science and Technology Centers at the Children's Hospital of Philadelphia and at the Whitehead Institute for Biomedical Research in Massachusetts, published a clone map of chromosome 22, making it the third human chromosome map to be completed.

Finding your way around a physical map also requires a set of markers. Using the STS (sequence-tagged site) system of markers, genome scientists have developed a physical map that currently contains about 15,000 markers, half the number needed to meet the goal. The goal of adding 30,000 STS markers to the physical map--one every 100,000 bases--will likely be met in the next few years. This detailed STS map will allow a skilled researcher to pinpoint the exact location of any gene within 100,000 bases of an STS marker. A recent initiative by private industry, which aims to produce short sequences of DNA from genes, will likely speed the rate of STS marker development and provide a resource for adding tens of thousands of markers from actual genes to the physical map.

NCHGR grantees have developed a new technique, called radiation hybrid mapping, for putting markers on the physical map of the whole human genome. Because of the complexity of physical maps, it is advisable to have more than one method available so that the accuracy of the map can be checked in two different ways. The application of radiation hybrid mapping will also expedite completion of the map.

The detailed maps coming out of the Human Genome Project will be critical to understanding the basis of many of the common diseases affecting Americans today, which are complex disorders that result from effects of multiple genes as well as environmental influences. This past year, for example, a researcher used genetic maps to discover at least five different chromosome regions that appear to play a role in insulin-dependent (type 1) diabetes. This kind of genome scan would not have been possible without high-resolution genome maps. The maps will be invaluable in teasing apart the contributions of genes to other complex disorders, including heart disease, asthma, cancers, and psychiatric disorders.

Genome technologies played a key role this year in the isolation of 13 disease genes, including a gene for hereditary breast cancer, BRCA1. While this number is dramatically higher than for years that predate the genome project, it is still a small fraction of the 50,000 to 100,000 genes that await discovery in the entire genome. NCHGR has helped to develop efficient biological and computer techniques to identify all the genes in large regions of the genome. One of these techniques, known as exon trapping, was used successfully this year to isolate BRCA1. Once the location of the gene was narrowed to within several hundred thousand bases, researchers still had to identify and examine each gene in the region to select the correct one. While exon trapping eventually turned up BRCA1, it also identified a number of new genes in that region, which now serve as candidates for future gene hunts. For example, a gene on chromosome 4, which was considered a strong candidate in an earlier search for the Huntington's disease (HD) gene, was eventually rejected because it contained no alterations in families prone to the disorder. When the gene for achondroplasia, which results in short stature, was mapped to the same general region on chromosome 4, the gene originally rejected as the HD gene was then reconsidered--and turned out to be responsible for achondroplasia. As our gene maps become denser, this kind of rapid disease-gene discovery will become more commonplace.

So we begin fiscal year 1996 having met or exceeded our original goals for mapping. We now turn our vision for the next phase of the Human Genome Project to the most challenging technological undertaking of all: determining the sequence of DNA bases in the entire 3 billion base-pair length of human DNA. Knowing the order of DNA bases tells an investigator where genes are located as well as what instructions are carried in a piece of DNA. This information is critical to understanding the function of genes and how they cause disease. To date, technology development for this work has been primarily carried out experimentally on the DNA of important model organisms. Researchers sequencing the genome of the roundworm have now amassed 10 million bases of DNA from that organism--about 10 percent of the animal's genome--and have increased their annual production rate from 2 million to 11 million DNA bases. These investigators expect to complete the sequence of the roundworm genome by the end of 1998.

Thus far, technology development in sequencing DNA has aimed at reducing cost and increasing rate. While cost has been lowered to that called for in the five-year plan, about $0.50 per base, the rate of sequencing is still slower than that needed to complete the human genome by the year 2005. NCHGR is therefore increasing emphasis in fiscal year 1996 on technology development for DNA sequencing to push the speed of sequencing using current gel-based technologies. This past year, NCHGR began a new initiative for development of microtechnologies to reduce the scale of sequencing instrumentation and therefore increase the speed of the sequencing process. For example, very small capillary or ultra-thin gels have been shown to be capable of increasing the rate of sequencing at least 10 fold. We will also explore new strategies for minimizing time-consuming bottlenecks by developing integrated, matched components throughout the sequencing process. The urgency of pushing these advances now is considerable. Every reduction in cost of 1 cent per base pair will save $30 million in the production phase of human DNA sequencing. An increase of $8.7 million has been requested in the FY 1996 NCHGR budget to support expansion of this critical initiative.

Success in developing good maps and other methods for rapid gene isolation makes preparing for the social impact of genetic information more urgent than ever. Among the most important issues is the responsible introduction of technologies arising from gene discoveries, such as genetic tests, into medical practice. Last spring, NCHGR's Advisory Council issued a statement urging that genetic tests for predisposition to cancer not be introduced into general medical practice until several important questions could be answered. Shortly after the isolation of BRCA1 and several important genes for colon cancer predisposition, NCHGR's Ethical, Legal, and Social Implications Branch spearheaded a new group of studies to examine the psychosocial and patient education issues related to testing healthy individuals from cancer families for the presence of mutations that greatly increase their risk of developing cancer.

These three-year studies will provide a well-researched knowledge base on which to build plans for introducing genetic tests for cancer predisposition into medical practice.

Commercialization of genome technologies has continued to increase as more private firms recognize its business potential. Collaborations with industry are occurring in NCHGR-supported university labs, our own Division of Intramural Research, and in cooperation with other federal agencies. Areas of product development include instrumentation, diagnostic tools, therapeutics, and research probes.

NCHGR's Division of Intramural Research has had a highly productive year in recruiting world-class scientists and putting genome technologies to use in deciphering the biology of inherited and acquired genetic disease. Unlike NCHGR's Division of Extramural Research, which maintains a tight focus on building the infrastructure of maps, DNA sequence, and technologies outlined in the Human Genome Project five-year plan, the focus of Division of Intramural Research is to apply these tools to the understanding, diagnosis, and cure of specific genetic disorders. Scientists in that division, founded just two years ago, have mapped or isolated a number of disease genes, including those for familial melanoma, Wolfram syndrome, and achondroplasia, a growth disorder that results in short stature. They also are developing new DNA-based methods for diagnosis and treatment of genetic disorders. New studies are underway to identify the genetic components of prostate cancer, the most common cancer in men, and of adult-onset diabetes, which affects about 6.5 million Americans.

In continued studies of families carrying the BRCA1 gene, intramural scientists have discovered a wide range of different mutations in that gene that predispose to breast cancer. The large size of the gene and range of these mutations complicate strategies for a general test for BRCA1. Similarly, NCHGR intramural scientists studying the genetics of other cancers have developed technologies for identifying chromosome alterations associated with melanoma, prostate, breast, and ovarian cancer. Powerful techniques for isolating the regions containing these alterations now make them available for studying how these cancers progress in people susceptible to the disorders.

This year the new intramural Medical Genetics Branch received approval to begin clinical research on familial nerve and connective tissue disorders, inherited immune system disorders, and congenital malformation syndromes. In addition, the branch has now established a first-rate training program for physicians and researchers in medical genetics and in genetic counseling.

The ultimate goal of genome research is to provide the fundamental understanding to enable researchers to develop prevention strategies, treatments, and even cures for genetic disease. NCHGR intramural scientists are at the forefront of gene therapy research for certain rare disorders, as well as common ones, such as AIDS and cancer. A new gene therapy trial has just begun for treating AIDS by inserting anti-HIV genes into the cells of AIDS patients. These genes block replication of HIV within the cells, which may help prevent the collapse of the immune system.

The Division of Intramural Research was also envisioned to be a resource to NIH laboratories, providing state-of-the-art expertise in various aspects of DNA mapping, gene analysis, the study of inherited disorders in families, and clinical training in medical genetics. This year, researchers in the division have participated in over 40 research collaborations across the NIH.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1996 is $166,678,000. I will be happy to answer your questions.

FRANCIS S. COLLINS, M.D., PH.D

Director, National Center for Human Genome Research

April 14, 1950. Staunton, Virginia

Education:

University of Virginia, 1970 - B.S. (with Highest Honors); Yale University, 1972 - M.S.; Yale University, 1974 - Ph.D.; University of North Carolina School of Medicine, 1977 - M.D. (with Honors)

Professional History:

1976-1977, Fellow in Genetics and Biochemistry, University of North Carolina School of Medicine, Chapel Hill, North Carolina. 1977-1978, Intern in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1978-1980, Assistant Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1980-1981, Chief Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1981-1984, Fellow in Human Genetics and Pediatrics, Yale University School of Medicine, New Haven, Connecticut. 1984-1988, Assistant Professor of Internal Medicine and Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan. 1987-1988, Assistant Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1987-1991, Chief, Division of Medical Genetics, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. 1988-1991, Associate Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1988-1991, Associate Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1991-1993, Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1991-1993, Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1993 to present, Director, National Center for Human Genome Research, NIH, Bethesda, Maryland.

Board Certification:

Board of Medical Examiners, State of North Carolina, 1977
American Board of Internal Medicine, 1980
Board of Medical Examiners, State of Connecticut, 1981
American Board of Medical Genetics, 1984
Board of Medical Examiners, State of Michigan, 1984

Professional Organizations:

American Association for the Advancement of Science; American Society of Human Genetics, Human Genome Committee, Ad Hoc Committee on Cystic Fibrosis Screening, Board of Directors; American Scientific Affiliation; American Federation for Clinical Research; American Society for Microbiology; American Society of Hematology; American Society for Clinical Investigation; Human Genome Organization (HUGO), Executive Council; Institute of Medicine; National Academy of Sciences.

Editorial Boards.

Associate Editor, The American Journal of Human Genetics, 1986-1989. Currently: Associate Editor, Genomics; Associate Editor, Technique; Associate Editor, Genes, Chromosomes, and Cancer; Associate Editor, Somatic Cell and Molecular Genetics; Associate Editor, Human Molecular Genetics; Associate Editor, Human Mutation

Awards and Honors:

Dean's Prize for Academic Excellence, 1970; National Science Foundation Graduate Fellowship, 1970-1973; Morehead Foundation Fellow, 1973-1977; Alumni Loyalty Merit Award, 1974; Deborah C. Leary Research Award, 1975; First Prize, Student Research Day, 1975; Riggins Scholarship, 1975; Heusner Pupil Award, 1976; W. Reece Berryhill Scholarship, 1976; Medical Faculty Award, 1976; Isaac Hall Manning Award, 1977; Alpha Omega Alpha, elected Junior year, President of UNC chapter, 1976-1977; Intern of the Year Award, 1978; Henry C. Fordham Senior Resident Award, 1980; Charles E. Culpepper Foundation Fellow, 1983-1984; Cooley's Anemia Foundation Fellow, 1983-1984; Anthony Renda Research Grant, 1984-1985; Hartford Foundation Fellowship, 1985-1987; Jerome Conn Research Award, 1986; Paul di Sant'Agnese Award of the Cystic Fibrosis Foundation, 1989; Honorary Doctor of Science, Emory University, 1990; James A. Shannon Lecturer, Massachusetts General Hospital, 1990; Elizabeth Crosby Teaching Award, 1990; Gairdner Foundation International Award, 1990; Von Recklinghausen Award of the National Neurofibromatosis Foundation, 1990; Michiganian of the Year, The Detroit News, 1990; Lynen Medal of the Miami Bio/Technology Symposium, 1991; Young Investigator Award of the American Federation for Clinical Research, 1991; Honorary Doctor of Humane Letters, Mary Baldwin College, 1991; Doris Tulcin Award for Cystic Fibrosis Research, 1991; Elected to Institute of Medicine, 1991; Distinguished Faculty Achievement Award, University of Michigan, 1991; National Medical Research Award, National Health Council, 1991; Dickson Prize, University of Pittsburgh, 1991; Association of American Physicians, 1992; Honorary Doctor of Science, Yale University, 1992; Honorary Degree of Doctor of Science, The Mount Sinai Medical Center, 1993; Jack Saint Clair Kilby Award, 1993; Kaiser Permanente Award for Excellence in Teaching, University of Michigan, 1993; National Medical Research Award (as member of Huntington's Disease Collaborative Research Group), National Health Council, 1993; Sarstedt Prize for Scientific Research, Dresden, Germany, 1993; CIBA-Geigy/Drew Award in Biomedical Research, Drew University, 1993; John M. Nokes Lecture, University of Virginia, 1994; National Organization for Rare Disorders Scientific Leadership Award, 1994; Honorary Doctor of Science, University of North Carolina-Chapel Hill, 1994; Nelson Award, University of California-Davis, 1994; Lovelace Institute Award for Excellence in Environmental Research, 1994; George D. Aiken Lecture, University of Vermont, 1994; American Academy of Achievement Golden Plate Award, 1994; Steven C. Beering Award for Outstanding Achievement in Biomedical Science, Indiana University, 1994; The Baxter Award for Distinguished Research in Biomedical Sciences, Association of American Medical Colleges, 1994; Willis M. Tate Distinguished Lecture, Southern Methodist University, Dallas, Texas, 1994; Jean-Pierre Lecocq Prize, Transgene, S.A., Straussbourg, France, 1994; Lila Gruber Cancer Research Award, American Academy of Dermatology, 1995.

LEGAL AND ETHICAL IMPLICATIONS OF GENOME RESEARCH

Mr. PORTER. Yes, you certainly know how to get to a Chicagoan. Every time I drive down the outer drive past a beautiful lake shore, along Lake Michigan, most of which is in public hands and consists of parks and beaches, I thank God for Daniel Burnham and his thinking big, and making noble plans. And so we also appreciate that you are thinking big, and we want to think big with you and provide you the resources to do exactly that.

Can I ask first about, this is not to do with research, but this is about people like Beth. Are there any provisions in law or any restrictions on providing to someone like Beth the information that would reassure her in the event it was positive, or at least give her an understanding of the risks if it were negative? Is there anything now that is provided that controls the situation, or is it up to the individual physician?

Dr. COLLINS. I would say at the present time there are no legal constraints upon the provision of DNA testing to someone in that situation other than the quality control issues. The FDA has a mandate to oversee the production of kits that are being used for DNA testing. HCFA, the Health Care Financing Administration, has a mandate to inspect laboratories that are doing this kind of testing, with the intent of being sure that the testing is being done accurately and that the results can be trusted.

Both FDA and HCFA are anxious, I think, for additional input about how to carry out this role for this very new area of DNA testing. That is, in fact, one of the major mandates of the Genetic Testing Task Force, which I mentioned, and which will have its first meeting in the next month. This group will have representation from both of those agencies. This Task Force, which will be chaired by Dr. Neil Holtzman, a very respected geneticist at Johns Hopkins University, will be trying to answer your question in terms of the appropriate sort of oversight of this new and exciting but very powerful kind of testing.

I take the point of view that DNA testing has both risks and benefits, just like drugs. You wouldn't think of taking a drug from the chemistry laboratory and giving it to a patient in the doctor's office the next day. You would put it through clinical trials to find out what its benefits are and what its toxicities are. In the same way, I believe that DNA tests need to be evaluated on a pilot scale before they are applied on a large scale to patients in primary care physicians' offices.

Mr. PORTER. Dr. Collins, wouldn't you say we're a little behind the curve, since the technology is known, and the applications can be made now and there are no legal standards and there are no ethical standards at the present time, are there?

Dr. COLLINS. Several policy statements have been made. The Advisory Council of the National Center for Human Genome Research published a statement a year ago, stating that DNA testing for susceptibility to cancer is now a research tool and it should only be done as part of a research project with full informed consent. A similar statement was made by the American Society of Human Genetics, and a similar statement was made by the National

Breast Cancer Coalition with regard to the breast cancer gene, BRCA1.

So there is rather unanimous agreement that DNA testing is at the present time not ready for importation into primary care physicians' offices.

Mr. PORTER. So in other words, these problems are theoretical at this point in time, and the committee is on target?

Dr. COLLINS. That's right. But I think we have to move with alacrity in the next year or two, because the pressures, particularly from the private sector, in terms of providing these services, will grow. We need to be prepared with a full range of guidelines, and we need to have physicians educated about the appropriateness of these tests. I'm confident that we are on target, but we need to move swiftly.

GENE IDENTIFICATION

Mr. PORTER. In 1994, researchers isolated 13 disease-causing genes in what you are quoted as calling a spectacular year. Can you give us some idea where we stand now, how this compares to accomplishments of previous years and perhaps what we can expect this year? How many diseases are thought to be genetically linked? I think either you or Dr. Varmus said all disease may be genetically linked, or at least susceptibility to disease may be genetically linked.

Of those, how many have been identified to specific sites in the chromosome and for how many have the genes themselves been identified?

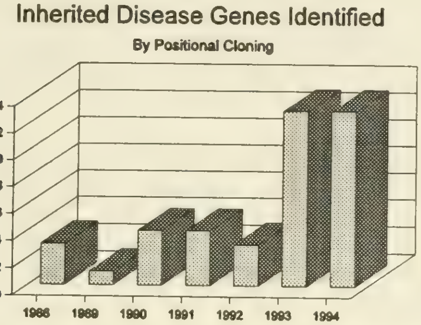
Dr. COLLINS. The statement you made about all diseases being genetic is one with which I would agree. I might make an exception, perhaps, for trauma, since in general that comes about as an environmental event and not as a genetic one, although you might argue that some people are more predisposed than others. But certainly for most medical illnesses, if you look hard enough, you can identify the fact that there are hereditary factors that are predictive of who is at greater risk and who is at less risk. And those interact with the environment.

Yes, it was a very good year last year in the identification by positioning cloning of 13 disease genes, which included important ones like the breast cancer gene, BRCA1. We were quite gratified by that, and I suspect 1995, which is already off to a very good start, will exceed that.

[The following information was provided subsequent to the hearing:]

GENE IDENTIFICATION

A number of disease genes have been discovered using different technologies over the years. The number for which positional cloning has succeeded in precisely identifying the responsible gene is about 50. Thirteen disease genes were identified in 1993 and 13 more in 1994 using this technique. In comparison, over the entire 7-year period, 1986-1992, a similar number (15) of disease genes were identified by the same strategy. The following graph indicates the sharp rise in gene identification.



The number of diseases for which genes have been mapped to general locations on chromosomes is in the hundreds. It is a very difficult number to keep track of, because it changes almost daily, but I would estimate close to a thousand at this point. The number for which positional cloning, the technique that I referred to in the opening statement about narrowing down the region and finding the right gene, has succeeded in identifying the gene is about 50. However, there are a large number of other disease genes that have been identified because we knew something about the biological problem, and that allowed us to get to the gene more quickly, and there are a few hundred of those.

Nonetheless, we are still ignorant about the genetic causes of many common diseases and there are thousands of those. That is the real challenge for the future, to figure out how to use these same techniques to identify genes that are responsible for diabetes, hypertension, coronary artery disease, schizophrenia and so on.

This has been an exciting year in that regard as well. For the first time, investigators have begun to map such genes. Perhaps the most impressive advance was identifying regions which contribute to juvenile onset diabetes using the same strategies that have worked for things like Huntington's disease and colon cancer. This research will continue to move forward. Thus, the most exciting set of developments over the next five years will be finding genes for common conditions that afflict millions and millions of people.

TARGETED CHROMOSOMES

Mr. PORTER. Is the project working on target-specific guidelines or general guidelines? In other words, are you mapping in a general way or are you looking at certain areas and saying, there's possibilities of finding disease susceptibility among these sets of chromosomes or genes, and working that way?

Dr. COLLINS. I think the problem with doing this sort of research in a targeted way is you never know which area of a chromosome is going to be interesting until it becomes interesting. The goal of the Human Genome Project, and one of the major rationales for its existence, is that it is more efficient to just do the whole thing. That has been the intent from the start, to get complete maps of the entire set of human chromosomes, both genetic and physical. Now we intend to put all the genes on those maps so we know where they are and to do it in a way that is not distracted by today's favorite exciting area. Because tomorrow's exciting area will be someplace else and we need to be prepared for that.

GENE DISCOVERY TO TREATMENT

Mr. PORTER. Is there any way to generalize about the likely time between the discovery of a disease gene and the development of some form of therapy or treatment?

Dr. COLLINS. That's a difficult question to answer, Mr. Porter. It will differ for each gene discovered. What you can say is that the discovery of a disease gene leads you fairly quickly to diagnostic capabilities, that is, the ability to identify misspellings in the gene and identify individuals with the misspelling which may place them or their children at higher risk. That will usually happen within the course of a year or two after a gene discovery. Whether you want to offer the diagnostic test depends on whether this is information that benefits people and that people want.

The use of the gene discovery, however, to develop treatments or cures for the disease, is a much less predictable path. It will be a different path for each gene, because it depends on which organ is affected, which cells in that organ are affected, what is the problem inside those cells—is it in the membrane, is it in the nucleus—and what strategies could be developed to fix the problem?

In some instances, like cystic fibrosis, for instance, there may be a gene therapy strategy where you take the correct gene and put it into the cells that need it in order to correct their defect. In other diseases, gene therapy may not be so successful, particularly in the case of dominant conditions. But in those instances, having the gene in front of you may also suggest a drug therapy that you could not have thought of without having the gene sequence. As for instance what is now happening in the cancer field and the RAS gene.

So the time is unpredictable.

Mr. PORTER. I want to call on Mr. Obey early, because I know he has a very busy schedule. Mr. Obey.

USE OF GENETIC INFORMATION

Mr. OBEY. Thank you, Mr. Chairman.

Doctor, people have talked about sequencing in dealing with this project. I'm concerned about a different kind of sequencing. Scientists are curious people. They lust for answers to questions. The problem is that they operate in a society which I don't trust very much. And they operate in a society in which the economy and the politics are often stacked against individuals and for institutions, especially big institutions.

And I think any time that you have a new piece of knowledge, it's an open question as to who is going to be able to wind up with the most power associated with that knowledge—employers, insurance companies, or individuals. A few years ago when Dr. Watson testified before us, I expressed a good deal of concern about the fact that the science was getting ahead of the ethics. And I still feel that way.

And I for one, though I am very interested in discovering everything that we can on this subject, I'm very concerned about the timing of that discovery if it races ahead of the ability of this society to deal with the ethical considerations associated with the discovery of that knowledge.

I know that you devote now a certain portion of your budget to dealing with these ethical questions, but I guess I would like to know what the real vulnerabilities are, as this knowledge expands. What kind of evaluation have you or your people done so that we understand what the state of the law is with respect to how insurance companies or how employers can use this knowledge.

I think that 99 times out of 100, employers and insurance companies will always win out in the political arena. And so I'm very concerned about developing knowledge before we have agreed how we're going to handle it. My grandmother used to tell me, "just 'cause you can do something, that doesn't mean you ought to."

Dr. COLLINS. I agree with that.

Mr. OBEY. I'm very reluctant, frankly, to put more money into this project until I am convinced that the Congress and State legislatures and governors and presidents and the best minds in science and law are focused on getting this up to speed and how we handle this information. What is the state of the law, at both the Federal and State level, and what kind of analysis have you people done of that, so that we have some idea of just how far behind the science the politics of this issue is?

Dr. COLLINS. Mr. Obey, you are right to raise these issues. And I think your voice has been an effective one in these discussions. I have read over the conversation you had with Dr. Watson in the past. My own view is that if we don't get this part of the Human Genome Project right, the public will not necessarily thank us. They will not benefit in the ways that we imagine they will. If this information is used to discriminate against people instead of to benefit them, then we will have committed an egregious sort of error.

I am incredibly committed to being sure that this part of the project goes well. As a physician who has spent hours in the genetics clinic talking to patients, some of whom have been damaged by discrimination on the basis of their genes, I agree with you that this should not happen, and that there are powerful forces arrayed to try to continue this discrimination.

The Human Genome Project does not introduce brand new dilemmas in this regard. What it does do is to accelerate the pace at which these discoveries are made.

Mr. OBEY. But it raises them to new, higher levels of reality.

Dr. COLLINS. Because more and more people are potentially at risk. I agree with you. However, on the major issues, I would like to be guardedly optimistic with you, because we have made substantial progress in the last four years.

STATUS OF LAWS

Mr. OBEY. I'm looking for specifics. Have you analyzed, on a State-by-State basis, the state of law with respect to the use of this information by insurance companies or employers?

Dr. COLLINS. We have.

Mr. OBEY. How would you describe the state of the law?

Dr. COLLINS. Okay, let's begin with health insurance. Health insurance discrimination on the basis of genotype is occurring. It is not currently widespread, because most people have not had this sort of testing yet.

But Dr. Paul Billings and other investigators like him, who have been collecting case studies, can cite to you perhaps a hundred or more instances in which individuals have had their health insurance taken away from them as a consequence of the results of a genetic test. Many of these people have been tested for Huntington's disease.

Mr. OBEY. Would you place all of those in the record, please?

Dr. COLLINS. Those cases?

Mr. OBEY. Yes.

Dr. COLLINS. We certainly can do that.

[The information follows:]

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Discrimination as a Consequence of Genetic Testing

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Summary

Genetic discrimination refers to discrimination directed against an individual or family based solely on an apparent or perceived genetic variation from the "normal" human genotype. We describe here the results of a case history study designed to assess whether or not genetic discrimination exists. Using the above definition of genetic discrimination and applying stringent criteria for case selection, we find that genetic discrimination exists and is manifested in many social institutions, especially in the health and life insurance industries. Stigmatization, and denial of services or entitlements to individuals who have a genetic diagnosis but who are asymptomatic or who will never become significantly impaired, is noted. Follow-up comprehensive studies on the significance and varieties of genetic discrimination are needed. In order to avoid creating a new social underclass based on genetic discrimination (the "asymptomatic ill"), existing and future genetic testing or screening programs need review by medical, scientific, legal, and social policy experts, as well as the public, and may require modification.

Introduction

The accelerating development of biochemical and DNA-based diagnostic tests for human genetic conditions in the last decade has engendered a revolution in genetic diagnosis. Numerous families faced with agonizing clinical or family planning decisions have been aided by information obtained through these tests (Phillips 1988). With further refinement of the human genetic map (Donis-Keller et al. 1987; McKusick 1988), the limited repertoire of genetic tests for the predisposition to common conditions such as cancer, cardiovascular diseases, and mental disorders may markedly expand (Lander and Botstein 1986; Scott 1987).

Insurance companies, private employers, governments and educational institutions all have an immediate or potential interest in promoting large-scale genetic screening to identify individuals carrying disease-associated genes (Motulsky 1983; Murray 1983; Uzych 1986; Hewitt and Holtzman 1988; Holtzman 1988, 1989; Nelkin and Tancredi 1989; Office of Technology Assessment 1990; Natowicz and Alper, in press). In addition, economic pressures to apply genetic tests to broader sections of the population may increase as biotechnology companies develop and sell genetic testing products and services (Hewitt and Holtzman 1988). Finally, the pace of development and application of DNA and biochemical genetic tests and their acceptance by the public may be accelerated by the recent widespread media coverage of the work of human geneticists.

As a result of the pressures to implement genetic technologies, problems engendered by their application may be overlooked. For example, with relatively few exceptions, our knowledge of how genes produce clinical illnesses is still quite limited. Yet an evaluation of the predictive value for clinical disease, utility, and impact is necessary before general use of genetic tests

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can be endorsed. In addition, some authors fear that an uncontrolled use of the tests may lead to a revival of social policies based on eugenics (Kevles 1985).

While there have been theoretical concerns about prejudices and discrimination surrounding genetic conditions, few investigations of these issues have been published (Hampton et al. 1974; Motulsky 1974; Kenen and Schmidt 1978; Murray 1991). Studies on the impact of genetic counseling have generally focused on subjects' understanding of genetic information and on family planning decisions (Leonard et al. 1972; Evers-Kiebooms and van den Berghe 1979); evaluations of the impact of genetic screening programs are typically concerned with issues of diagnostic sensitivity and specificity, medical efficacy, and cost-effectiveness and have usually not assessed long-term nonclinical outcomes. The personal costs of consenting to genetic testing and screening have not been studied and raise many issues of considerable significance.

Given this situation—powerful and attractive new techniques, social and economic forces pressing for their application, and an incomplete understanding of the potential negative social and personal consequences of genetic testing—concern about the burdens engendered by widespread utilization of genetic tests seems justified. One such issue is the problem of genetic discrimination.

This paper describes the results of a preliminary study of individuals labeled with genetic conditions. This study is not a survey; it does not purport to give statistically significant information about the extent of genetic discrimination. Instead, the aim of the study was to discover whether incidents which may reflect genetic discrimination are occurring in the workplace, in access to social services, in insurance underwriting, and in the delivery of health care. If the existence and range of genetic discrimination revealed by this study are confirmed by other investigations, then current policies and practices regarding the application of genetic testing and utilization of information obtained from such testing may need to be reconsidered.

Methods

A definition of genetic discrimination was developed for this preliminary study based in part on the work of the Genetic Screening Study Group, a Boston-based public interest group (Dusek 1987; Billings 1989; Beckwith 1991; Natowicz and Alper, in press). Discrimination stemming from supposed hereditary transmission of a condition can be obvious, as in the case of an individual who was denied a job because a health record noted that the applicant's mother was "schizophrenic." In other instances, the distinction between discrimination based on clinical disability or illness, and that arising from genetic aspects of a condition, may be more difficult to determine. For the purposes of this study, genetic discrimination is defined as discrimination against an individual or against members of that individual's family solely because of real or perceived differences from the "normal" genome of that individual. Genetic discrimination is distinguished from discrimination based on disabilities caused by altered genes by excluding, from the former category, those instances of discrimination against an individual who at the time of the discriminatory act was affected by the genetic disease.

An advertisement to solicit cases of possible genetic discrimination was mailed to 1,119 professionals working in the fields of clinical genetics, genetic counseling, disability medicine, pediatrics, and social services in New England. This solicitation was also published in the American Journal of Human Genetics (Billings 1988). Similar appeals were reprinted in newsletters of organizations of individuals with genetic conditions, such as associations for persons with Friedreich ataxia, Charcot-Marie-Tooth disease (CMT), and muscular dystrophy.

Many responses included supporting documentation. Each described incident was reviewed independently by two of the authors (P.R.B. and M.A.K.), and a decision was reached as to whether it met the standard for inclusion in our study. This preliminary investigation was closed after receiving responses for 7 mo.

The most common reasons for excluding responses in this study were that (1) the differential treatment was based on a physical variation or disability (for example, individuals with Turner syndrome who were discriminated against in employment because of short stature), (2) there was a lack of evidence that the differential treatment arose from the hereditary nature of the condition, and (3) there was inadequate information submitted to determine whether discrimination had occurred.

Results and Discussion

Of the 42 responses received, 13 (31%) were excluded from further study because of failure to meet our strict criteria for genetic discrimination or because insufficient information was provided to enable an accurate assessment. The remaining 29 responses came from all regions of the United States and Canada. A variety of genetic conditions were represented in the study group, including Huntington disease, Friedreich ataxia, CMT, hemochromatosis, phenylketonuria (PKU), and others. Most of the responses were elicited by the advertisement reprinted in newsletters.

The 29 evaluated responses described 41 separate incidents of possible discrimination. Of these 41 incidents all but two involved insurance or employment. Thirty-two incidents involved insurance (applications or coverage changes for health, life, disability, mortgage, and auto insurance), and seven involved employment (hiring, termination, promotion, and transfer).

The respondents described difficulties in obtaining desired insurance coverage, in finding or retaining employment, and in interactions with adoption agencies. Problems with insurance companies arose when individuals altered existing policies because of relocations or changes of employers. New, renewed, or upgraded policies were frequently unobtainable even if individuals labeled with genetic conditions were asymptomatic. Assessment of the natural history of the genetic condition or evaluation of the fitness of the individual by physicians had little or no influence on the adverse outcomes presented by the respondents. Because of fear of discrimination, several respondents reported that they withheld or "forgot" to mention potentially important medical or family history information to physicians, employers or insurers. Others reported that their insurance agents suggested that they give incomplete or dishonest information on insurance application forms.

The responses excerpted below illustrate several themes that appeared repeatedly in the data. These themes can be grouped into three categories: (1) "The Asymptomatic Ill," (2) "The Problem of Variability," and (3) "The At-Risk: to Test or Not to Test? Dilemma." While the incidents suggest discrimination by specific institutions such as insurance companies, the cases and types of genetic discrimination described below may reflect the attitudes and practices of an array of business, social, and political institutions.

The Asymptomatic Ill

Many individuals identified as having a hereditary condition are healthy. Some have undergone testing only because other affected family members have been identified with a genetic condition. As the number of genetic tests increase, and are widely applied, an increasing number of individuals will discover that they harbor a disease-associated gene but have no identifiable clinical illness.

A respondent from a family with hereditary hemochromatosis wrote: "In 1973, at age 27 and 1/2, I was diagnosed as having excessive iron storage and was put on a regime of phlebotomies. . . .

"[After several years] I have never had the slightest symptom, in part because early detection [and appropriate treatment] of iron overload in my case avoided damage. . . .

"[After failing to get insurance because of my hemochromatosis] I have supplied doctor's testimonies to no avail. I might as well have AIDS. Even though I have proven that I prevented health problems by early detection and prophylaxis, they condemn me to the same category as lost causes. I run 10 Km races, etc. I am not a basket case, and will not be one, ever, because of iron overload."

With respect to a second case, a physician reported that "an individual was found to have Gaucher Disease. His brother was screened and the results were consistent with unaffected carrier status [heterozygote]. The brother applied for a governmental job and included the history of his testing in the application. He was denied the job because of his being a 'carrier, like sickle cell'."

With respect to a third case, a clinical geneticist caring for individuals with PKU wrote: "[Name withheld] is an 8 year old girl who was diagnosed as having PKU at 14 days of age through the newborn screening program. . . . A low phenylalanine diet was instituted at that time. . . .

"Growth and development have been completely normal. Height, weight, and head circumference all follow the 25th percentile. Routine developmental assessments done at 26 weeks, 53 weeks, and 54 months revealed skills solidly appropriate for age, and in many instances skills were above age-expected levels. The child continues to be developmentally normal and be healthy. The circumstances of the discrimination that this child has experienced involve rejection for medical insurance. She was covered by the company that provided group insurance for her father's previous employer. However, when he changed jobs recently, he was told that his daughter was considered to be a high risk patient because of her diagnosis, and therefore ineligible for insurance coverage under their group plan. She is currently being covered at the expense of her family, but this is a temporary solution at best. The family has written to the agency that administers the group insurance plan to obtain details of the decision to deny coverage and also plans to write to the chairman of the large corporation for which the father works. All information will also be submitted to the [state] insurance commissioner."

Comment

The first case illustrates both the promise and the burden of genetic testing. It was through genetic testing that this individual was diagnosed and successfully treated. Yet, because of his test results, he has been stigmatized and denied insurance as if he were severely ill. Similarly, the individual described in the second case was denied employment because of his genotype, despite the fact that he was asymptomatic and a heterozygote for an autosomal recessive condition.

The third case illustrates both the benefits of genetic testing in enabling the early detection and successful treatment of many children with PKU and constraints that can be imposed by genetic labeling. The cost of a phenylalanine-restricted diet, an effective treatment for PKU, is high. Without insurance, it is possible that the family would not be able to afford treatment for their child, with the consequent risk of developmental delays and permanent impairment. The family's life is restricted by the necessity for the father to maintain employment in the same state and at the same job in order to have access to insurance. Thus, the child's diagnosis has a major impact on the geographic and job mobility of other family members. These constraints, in turn, could cause economic or other potentially significant limitations.

By preparing to take their situation to a state agency, this family demonstrated "self-advocacy" abilities. The poor, the uneducated, foreign nationals, or those with fears about their job security may not be as willing or able to negotiate the complexities of our legal and regulatory systems in order to secure their rights.

All three cases illustrate instances of discrimination against individuals who are completely asymptomatic; their only "abnormality" lies in their genotypes. As large numbers of individuals submit to or are coerced into testing in order to obtain employment or insurance coverage, a new social class and category—the "asymptomatic ill"—may be constructed. Although they are healthy, persons in this new group may find that they are treated as if they were disabled or chronically ill by various institutions of our society (Marx and Sherizen 1986; Nelkin and Tancredi 1989).

All of the cases suggest that access to jobs, insurance, or social entitlements may be limited because of genetic discrimination. Stigmatization and frustration ("I might as well have AIDS") may accompany the test result. The financial and legal burdens of maintaining a reasonable standard of living and basic entitlements as a result of genetic discrimination could be significant.

The Problem of Variability

Several responses described situations in which people were victimized because of a misunderstanding of the clinical variability of many genetic conditions. One respondent with CMT, a nonfatal, clinically variable, and genetically heterogeneous neuromuscular condition, wrote: "I have been rejected for life insurance many times, but only once was CMT cited [explicitly] as the reason. . . . [I appealed, informing the insurance company] that people do not die from CMT and that they had declared me automatically eligible for accidental death insurance—the one risk that can be assumed might be greater for people with CMT. . . . [The insurance company's reply] repeated the statement that CMT is the reason for rejecting my application.

"In 1979 my daughter was denied employment by the [name omitted] Company because she has CMT even though the case is not really noticeable. She had indicated on the form that she had CMT and the examiner asked her what it stood for; then, he looked it up in a medical book and denied her a job which had been offered to her by the recruiter."

Another respondent stated: ". . . My husband has a genetic disorder, Charcot-Marie-Tooth. We have just been turned down for automobile insurance with [name omitted] because of his disease. I have just recently sent them a letter from my husband's doctor . . . explaining that my husband is a far better driver than anyone I know. . . . My husband has had NO accidents, or traffic violations since he has been driving from the age of seventeen [twenty years of driving]."

Comment

In these examples involving CMT, the individual does suffer from a disease, but the symptoms are mild. The decisions regarding life and automobile insurance, and employment, were based solely on a diagnostic label, without regard to the severity of the condition for each individual. In these and other cases, having a particular genotype is equated with the presence of a severe illness and the lack of effective treatments. This evaluation of genetic conditions illustrates a lack of understanding of the concepts of incomplete genetic penetrance, variable expressivity and genetic heterogeneity. In many cases, the worst possible scenario seems to be the standard used for policy decisions regarding at-risk individuals. Yet wide variation in clinical manifestations of a gene-associated disorder—individuality—is common. As highlighted in these examples, an individual may suffer serious consequences as a result of the inaccurate and unfair simplification of genetic conditions.

The At-Risk: to Test or Not to Test? Dilemma

The third category includes those individuals who are currently healthy but who may be at risk for a genetic disease. Discrimination may ensue as a result of a decision to forego testing and thereby not determine whether they (or their future children) will develop the disease. Discrimination may also occur if they opt for such testing and the results reveal a genotype associated with disease.

A respondent wrote: "I am at risk for Huntington Disease [age 31]. After many years of consideration, my husband and I decided not to bear our own children, but rather to adopt children, so as not to take the chance of passing on the Huntington gene.

"In 1987 we began investigating adoption. We encountered restrictions due to religion and availability of infants, but were finally invited to make application with [name and location of agency omitted]. We began our counseling process and our home visits, at which point the issue of my being at risk was discussed (I had disclosed in my original application the possibility of my developing the disease and why we had chosen adoption). Before completion of our home study, we were asked to withdraw our application, because of the Huntington Disease situation. . . .

"We understand the right to choose the BEST 50 couples out of some 500 applicants per year for placement. Availability of children is incredibly limited. And yet, should I be judged by a disease that I am only at risk for and that may not develop for some years to come? Does this make me different than anyone with diabetes or cancer, for example, in their ancestry?"

Another couple at risk for Huntington Disease sent a letter they received from an adoption agency: "We have decided, in your situation, not to proceed with your application because there is a fifty-fifty chance of your getting Huntington Disease. Though you would be likely to get the disease around the age of fifty, it could be sooner. You would not receive a child from us, if we could proceed with your application, for several years, and therefore we would be risking the likelihood of not having you available to the child until he/she has reached adulthood. We feel that a fifty-fifty chance of getting a disease as serious as Huntington Disease is too great a risk, for our purposes and circumstances."

In a third case, a physician informed us that "a family with a child who has cystic fibrosis received health care through an HMO. When a second pregnancy occurred, prenatal diagnosis using DNA analysis was instituted. Fetal DNA tested positively for two copies of a mutation associated with cystic fibrosis. Nevertheless, the family decided to proceed with pregnancy. After disclosure of the test result, the HMO considered withdrawal of or financial limitations on the health care coverage for the pregnancy, postpartum and pediatric care, as well as for the already affected child. Threats of legal action were required before this situation was resolved."

Comment

In the first two cases, the adoption agencies' attitude illustrates how certain conditions categorized as "genetic" are viewed as special and handled differently in terms of social decision making. The use of genetic tests to ascertain the genotype in such at-risk individuals will not necessarily lessen the chances of subsequent discrimination, since a positive test will not be an infallible predictor of the burden a genetic trait may place on an individual, nor does it predict the abilities of affected individuals as parents or the qualities of a potential home.

These incidents also illustrate a large eugenic prejudice—the myth of genetic perfection (Billings 1989; Suzuki and Knudtson 1989). The agencies assume that the best possible family is the one least likely to face medical adversity—the "perfect" family with a disease-free genome. Unfortunately, all families are at risk. The comparison made by one respondent, of being at risk for Huntington disease with susceptibility to diabetes or cancer, highlights a prejudice—that the chance of developing a genetic condition is perceived differently from a similar probability of contracting an illness not produced primarily by a gene.

The third case raises several social and ethical problems. The family was faced with the possibility that bearing a child with a certain genotype might reduce their access to necessary health care benefits. These circumstances constitute a strong incentive for aborting a fetus on the basis of its genotype, a practice that might be interpreted as a form of eugenics. Finally, the couple was forced to threaten legal action to avoid the abortion and loss of benefits, an alternative not available to people who cannot afford an attorney. In addition, pressuring a couple to have an abortion seems to infringe on a right many believe to be fundamental, the right to bear children.

Conclusions

This pilot study identifies multiple facets of genetic discrimination. It does not document the full range of the prejudices faced by individuals with genetic diagnoses, nor does it establish the prevalence of these attitudes or discriminatory practices. A comprehensive study of the significance and varieties of genetic discrimination is critical to design strategies to ensure the ethical and appropriate use of genetic testing in the future. The need for such studies is underscored by the large number of genetic tests currently performed each year. In addition, powerful business interests support larger applications of genetic techniques because of the revenues that tests and kits generate directly and indirectly.

The dominant theme noted in the responses in this study is that genetic conditions are regarded by many social institutions as extremely serious, disabling, or even lethal conditions without regard to the fact that many individuals with "abnormal" genotypes will either be perfectly healthy, have medical conditions which can be controlled by treatment, or experience only mild forms of a disease. As a result of this misconception, decisions by such institutions as insurance companies and employers are made solely on the basis of an associated diagnostic label rather than on the actual health status of the individual or family. The appropriate use of genetic testing information to restrict or limit access to public entitlements such as health care or employment has not been established and may not exist. The cost of such labeling is magnified by the fact that errors in testing and interpretation do occur.

Once labeled (possibly erroneously), an individual may suffer serious consequences, as highlighted in the examples. These include the inability to get a job, health insurance, or life insurance, being unable to change jobs or move to a different state because of the possibility of losing insurance, and not being allowed to adopt a child.

Furthermore, information related to genetic labeling may enter large-scale data banks now used to store personal health-related information. Individuals' health profiles, which can include genetic conditions, are available privately and are generated in a manner similar to the ubiquitous credit checks encountered in business. Breaches of confidentiality and unauthorized uses of this information may arise (Dezell 1984; Norton 1989; Billings 1990; DeGorgey 1990). Genetic data on certain groups within our society are already being stored by governmental agencies (DeGorgey 1990).

These incidents suggest that there are very important nonmedical reasons why individuals may wish to avoid genetic testing. It is clear that the option not to know is being exercised now. Many persons at risk for Huntington disease, for example, have refused to be tested (Meissen et al. 1988; Brandt et al. 1989). The choice to refuse testing will become more difficult if such testing is required for employment, to obtain affordable medical care, or to obtain or renew health or life insurance. The personal decision to undergo genetic testing certainly requires accurate information about the clinical predictive value of genetic tests (data which may not be available currently), but the widespread utilization of genetic testing as a prerequisite for obtaining social entitlements may also influence an individual's right to choose not to know his or her genetic predispositions.

Various constraints exist to prevent or limit abuses made possible by access to genetic information. These include, for example, laws affecting privacy and civil rights (Russell-Einhorn and Rowe 1989; Natowicz et al. 1992). In addition, limitations exist on the uncontrolled expansion of genetic testing and screening. These include opposition by individuals and interest groups (such as labor unions and disability advocates) sensitized by the dismal history of eugenics movements and suspicious of genetic and scientific incursions into normal daily life, economic constraints (i.e., the poor profit yield of some tests), and state and federal regulations regarding testing and screening.

Nevertheless, it is clear that unfair and discriminatory uses of genetic data already occur under current conditions. Enacted state and federal laws are inadequate to prevent some forms of genetic discrimination, particularly that due to the health insurance industry (this report; Natowicz et al. 1992). The implementation of carefully considered legislation regarding, for example, the privacy of genetic information and the imposition of meaningful penalties on social institutions such as insurers that are found guilty of genetic discrimination are mechanisms to address aspects of genetic discrimination. Consideration of alternative medical care systems is another potential approach toward solving some of these issues. Any approach should include the reaching of a broad-based public consensus on the appropriate use of genetic tests. Without further changes in social attitudes, legal protection, and/or changes in the prevailing American health care system, many healthy and potentially productive members of our society will suffer genetic discrimination.

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Dr. COLLINS. Now, what's being done about discrimination in health insurance. On the State level, there are now seven States, and I regret I don't know exactly which ones they are right now, but I can put that in the record, that have passed legislation. Some States make it illegal for health insurance agents to remove coverage on the basis of a genetic test that predicts a future susceptibility to illness.

[The following information was provided subsequent to the hearing:]

STATUS OF LEGISLATION ABOUT GENETIC DISCRIMINATION

In the past three years, at least seven states have recognized the potential for discrimination. At the forefront is Wisconsin, which prohibits health insurers from requiring genetic tests and forbids employers from demanding that job applicants undergo such screening. Iowa, Oregon, and Rhode Island passed similar rules covering only employers. California and Ohio enacted new laws last year concerning health insurance but allowed companies to ask for genetic tests when deciding on coverage for disability or life insurance. Florida has passed laws outlining requirements for informed consent on genetic testing. Lastly, many more states have legislation offering protections for carrier status.

Many of us who were working very hard on this issue last year were excited to see that the major health care reform bills included this issue as part of their language. These bills would have solved this very unfortunate situation at the Federal level.

With the collapse of that effort, many of us are working hard this year to see if there's a possibility in this Congress for Federal legislation on health insurance reform, especially in terms of removing pre-existing condition exclusions and increasing portability. If you have ideas about ways that we could be more effective in that regard, I would love to hear them. There does seem to be some bipartisan support for doing this this year. But obviously, people are quite distracted by other things.

Mr. OBEY. I think there is nominal support on both sides of the aisle for doing things like that. But the insurance companies, in the end, without a spectacularly well-organized effort, are going to win this argument, and so will employers.

Dr. COLLINS. The insurance companies have lost the argument in these seven states. And there are many other states now considering similar legislation. If we have to do it at the state level, this paradigm in those states demonstrates that it is possible to overrule those special interests by the passage of such legislation.

Can I go on to employment?

EMPLOYMENT ISSUES AND GENETIC INFORMATION

Mr. OBEY. Sure.

Dr. COLLINS. In the area of employment, serious concerns have been raised that individuals who are found to be at risk for future illness will either not be promoted or will lose their jobs, because their employers have anxieties about their abilities to lead an organization, or about the health care costs that they may incur. That has been an area where there was previously no protection. Passage of the Americans with Disabilities Act led to some optimism that this type of discrimination would be covered.

I'm happy to say, however, that only ten days ago, the Equal Employment Opportunity Commission issued their formal interpretation of the ADA, which makes it very clear that individuals who have had a test that says that they are at some future risk for genetic illness, but are currently well, are in fact covered by the ADA, making that quite explicit. I have not had that language interpreted by enough people to know whether there are still loopholes in it. But it looks extremely promising. I believe this is a major victory in the area of employment discrimination, and it did not happen accidentally.

So in that area, I think we have made substantial progress, and without the requirement of additional legislation. Simply by recognizing that the intent of the ADA had in fact been, all along, to cover such people.

PRIVACY ISSUES

Privacy is another important area to consider. Our medical records system in this country is not a private one. If somebody wants to find out your health history and they're motivated enough, they can get into your medical records and learn what disorders your family had and what you're at risk for. Last year there was a bill in the Federal legislation process to deal with this. It did not come through because it was attached to health care reform. But it was a start.

Meanwhile, the states have also taken up this issue. As part of the ELSI program, a model privacy bill has been produced by one of our grantees, a very respected lawyer named George Annas. That model bill is being considered now in a number of states, and seems to have a reasonable chance of passing. It may be that these issues are more effectively dealt with at the state level, even though that requires doing it 50 times instead of once. If there are ways to get these issues higher on the agenda of this Congress, again we would be delighted to know about them. But we're not necessarily depending on it.

PROTECTION OF GENETIC INFORMATION

Mr. OBEY. What if no grants were allowed from NIH to any recipient in any state that did not have laws actively protecting the use of that information?

Dr. COLLINS. I would be very troubled by that mechanism. I understand what you are saying, and it would be a very strong way of twisting the arms of the states. But who would be penalized? Investigators who happen to live in those states, and who have no particular control over the situation.

Mr. OBEY. I don't think so. The politicians would be in the hot seat so fast that they would get off their duffs and deal with the problem before it gets away from them.

Dr. COLLINS. I hope you're right. But what would be the consequences in the short term to investigators who have good ideas, to patients who are waiting for these research breakthroughs in order to save their lives or that of their children? You are proposing that maybe we should slow down the science and get the ethical issues and legal issues in order. But in the process, we would in some way be taking away hope from people who are living with these diseases right now. Their hope is in this research. Are we to hold them hostage on the basis of these concerns about the future ethical, legal and social consequences? That seems to me unethical.

Mr. OBEY. Well, I don't think you're holding anybody hostage. I think you're trying to protect the interests of the persons who are supposed to benefit rather than be damaged by this information.

So you don't believe it would be appropriate to require that legal protections be provided before new screening tests are approved by the FDA, for instance?

Dr. COLLINS. Well, in fact, those legal requirements exist. The FDA is not to approve kits for diagnostic testing until they have gone through the evaluation process to show that they're safe and efficacious.

Mr. OBEY. No, I mean the broader legal protections that I'm talking about.

Dr. COLLINS. I think we still have——

Mr. OBEY. I mean, I honestly don't believe that the ethics is ever going to catch up with the science unless we find some way to leverage people into moving forward on this issue. I mean, you have a hell of a lot more faith in the ability of this society to resist people with economic power than I do.

Dr. COLLINS. Two or three years ago before living in the midst of this set of dilemmas and debates, I would have shared your same concern, namely that we're not going to be able to pull this together until there's a crisis, until peoples' lives have been damaged. I am more optimistic now, because I can see the momentum that is underway. I think the health care reform debates had a lot to do with this momentum. People are beginning to grasp the idea that we all have pre-existing conditions written into our DNA, and the information is going to get used against us if we don't do something about it.

Momentum is building. We are not in a static position. The advances that have already been made in getting these protections in place are substantial. It is still true that widespread genetic testing for colon cancer or for breast cancer is in the future. It is not being done at the present time as part of primary care practice.

We still have a period of a couple of years to get these issues resolved. And I think there is a reasonable chance we will be able to do that. If we do not have the protections in a couple of years, then I think we may have the potential for trouble.

Mr. OBEY. Well, would you be willing to settle for that arrangement, if we don't have adequate protection in place in two years at the state and Federal level, that we halt funding for your project?

Dr. COLLINS. No, sir, I would be very uncomfortable with that plan. Perhaps if we don't have all the protections in place at that time, we should make sure that these genetic tests are not being allowed on a large scale. That makes sense.

But to slow down the basic science in order for that step to be achieved, will delay the entire Human Genome Project. Suppose you then get those protections in place the next year. You've lost that year. Such a linkage bothers me.

[The following information was provided subsequent to the hearing:]

DELAYING THE HUMAN GENOME PROJECT

Delaying the basic science until the ethical, legal, and social protections are developed and put into legislation will delay the entire Human Genome Project. International partners will not slow down their efforts. The level of support by other countries continues to grow, in the United Kingdom alone an increase of over 83 percent was budgeted for 1994–1995 for the Human Genome Project. The hopes of patients with a genetic disease and their families will be dashed if we slow the scientific research.

Mr. PORTER. This is a fascinating discussion, but it's Mr. Istook's turn. Mr. Istook.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

Mr. ISTOOK. Well, I may extend it in some way or the other. But let me ask a couple of questions first, recognizing, Dr. Collins, of course, that there have been many varied ethical issues that have been raised, has there been some sort of advisory panel or other mechanism to develop a checklist or repository of what you see as the ethical issues raised?

I'm not talking about where you come down on which side of some of them. But what is out there as far as a compilation of those issues? Have you done that through an advisory panel in documentary form, or how?

Dr. COLLINS. I think Dr. Watson deserves credit for pointing out the ethical issues and making them part and parcel of the project. On the very first day of the Human Genome Project, the ELSI working group was set up to advise on these issues. This group was chaired by Dr. Nancy Wexler, who herself is at risk for Huntington's disease, which killed her mother. She is a respected psychologist and researcher as well.

That working group met, and defined and prioritized the high-priority issues that the Human Genome Project needed to research. That agenda became, then, the blueprint for our ELSI research portfolio, which has funded a number of investigators to look into those areas and try to collect real data. For instance, what do people think about these issues? How much do primary care physicians know about genetics, and what are they telling their patients?

Grants in specific areas like cystic fibrosis carrier testing, which is being proposed in some areas, have been funded. Do people really want this information? How could it be given to them in ways that make sense to them? How do you ensure that you don't force the information on them if they're not interested in the first place?

Mr. ISTOOK. My question is, though, do you have something that is intended to be an all-inclusive report or discussion of the various ethical issues—whether it was at the original stage of the project, or more recently—that have been highlighted and surfaced as ethical issues? Do you have that assembled in one particular set of documents?

Dr. COLLINS. Yes. The initial list of issues is prioritized as part of our original five-year plan, which was published in October of 1990. When the Human Genome Project's five-year plan was revisited and revised in October of 1993, there was again a listing of the ELSI agenda and goals. This project has produced a number of specific documents that enumerate those ELSI issues.

I would like to particularly refer to an Institute of Medicine study which we funded called "Assessing Genetic Risks." This important document looks at the broad array of issues surrounding genetic testing, and makes very specific policy recommendations.

Mr. ISTOOK. But you're still not zeroing in on what I asked about. I'm not asking about discussion of all the varied implications or problems in human genome research. I'm talking about something that is a discussion focused on the ethical considerations. I would be interested in seeing whatever documents were developed and how you resolved those, at least for your own purposes. I think that would be a useful document. I would suspect that Mr. Obey would also be interested in that. Is there such a document or set of documents?

Dr. COLLINS. Well, there are documents. We are in the process this year of distilling our five years of ELSI research grants and identifying conclusions. That document is in draft form. It is not quite ready to be produced in a fashion that would necessarily clear up all the questions you are asking. But we would expect that it will be available in a few months.

Mr. ISTOOK. What's the status of that draft form? Is it, you say it's in a draft? Who's reviewing it or who's charged with changing it from a draft to something that has a final approval, and what's the time frame?

Dr. COLLINS. The ELSI working group will review it. This is our advisory body that reviews the entire ELSI arena. It consists of 15 members from a variety of walks of life, including consumers, professional geneticists, researchers, ethicists, philosophers, etc. This is the group which has asked for this report and which will be reviewing, modifying, and editing it. The time frame would probably be within the next 12 months. I'm a little loath to say exactly when.

Mr. ISTOOK. Do you currently have the draft?

Dr. COLLINS. No, the whole document has not yet been drafted.

Mr. ISTOOK. Realizing it is indeed in draft form and subject to change, but nevertheless, if there is something like that that highlights where people think they're coming down, I think that information will be very relevant to the Members of this subcommittee, because it does relate to the decisions that we have to make.

Dr. COLLINS. Again, Mr. Istook, the Institute of Medicine report has that characteristic. I did not mean to imply that it's just an enumeration of issues. It makes very specific policy recommendations. It reviews what's known and what is not known. It was just published in the last few months and has a very useful Executive Summary. We can supply that to you.

Mr. ISTOOK. Sure. If there's a mechanism that would be satisfactory to you, I think the information that's in the draft, since it is much more current, would certainly be useful to Members of this subcommittee. Perhaps we could discuss separately how that information should be conveyed without trying to publicly disseminate something that's a draft or give the impression that something is a final decision when it's certainly not.

Dr. COLLINS. Okay. I'm sure we can do that.

HUMAN EMBRYO RESEARCH

Mr. ISTOOK. Let me ask, is there any direct relation between the Human Genome Project and issues related to human embryo research? Is the use of that tissue relevant to the human genome project, or is that a different area?

Dr. COLLINS. It's really a different area. The Human Genome Project is devoted to developing maps and sequences of DNA. Embryo research covers a different, much broader area of issues. Dr. Varmus, as you know, has been very involved in reviewing that area, and if you have questions about embryo research, I would defer them to him.

RESEARCH GUIDELINES

Mr. ISTOOK. Sure. Before we do that, I wanted to establish first whether there was any direct connection there, because I know there are different legal as well as ethical issues. Are there any legal restrictions or impediments as you see them that directly relate to your ability to do the human genome research? Any significant or any important barriers there?

Dr. COLLINS. In terms of barriers that prevent the research from going forward at the speed one would like, I would not be able to identify specific legal impediments. There are certainly guidelines that we adhere to.

Mr. ISTOOK. Sure.

Dr. COLLINS. In fact, some guidelines we helped establish. For instance, genetic research on pedigrees and use of informed consent. We are very committed to those guidelines, but I would not call them barriers or impediments.

Mr. ISTOOK. Okay. I do have some questions for Dr. Varmus which relate to the human embryo, but I don't want to defer discussion at this time if there's other questions on it.

Mr. PORTER. Please proceed.

Mr. ISTOOK. Okay. Dr. Varmus, I know my office talked with you because there was a fairly recent report regarding the human embryo research which discusses ethical issues, similar to discussion that I'm asking about on the human genome. Can you give us, as far as the legal status under which human embryo research currently operates—whether it be limitations in appropriations bills or statutory restrictions—can you tell me basically what the status of that is?

Dr. VARMUS. As you know, Mr. Istook, until the NIH Revitalization Act of 1993, there was a ban on so-called in vitro fertilization research. That ban was lifted by the Revitalization Act. Before we undertook to fund research of that type, which as you know is being pursued in the private sector with considerable vigor, we assembled a panel of outside advisors, headed by Stephen Muller, previously the president of Johns Hopkins University, to examine many aspects of research on the pre-implantation embryo.

Let me make clear here that we're talking about the very earliest stages of life. We're talking about the human sperm and egg, the act of conception carried out in a petri dish, and the first divisions that occur after the entry of the sperm into an egg. At this stage, contrary to what might be the popular conception of an embryo as a small human being, we're talking about one, two, four, and eight cell aggregates that have no visible organs and no organization.

Dr. Muller's panel met many times over the course of a year, took a great deal of public testimony, heard many opinions, and presented to my advisory committee a set of recommendations, which I believe we supplied to your office last night.

Mr. ISTOOK. Yes. I have not had a chance to totally review them, just to skim.

Dr. VARMUS. The Director's advisory committee received the recommendations of the panel in early December, 1994. The panel members designated a number of research areas they felt were appropriate for funding by NIH, a number which they felt we should not consider for funding, and a number which they felt we should defer for consideration at a later date. They also recommended that we assemble a committee that at least for the next three years would review all grant applications in this area before they were funded.

My advisory committee unanimously accepted the report from the panel and also recommended that we establish an oversight committee that would, in addition to re-reviewing the grant applications, would help with public education in this area of research and give me advice about the general responses to what we should be supporting.

As you also probably know, on the 2nd of December, the President issued an executive statement that directed me not to provide any funds for research entailing the creation of embryos solely for research purposes. That left open the possibility of funding research with so-called spare embryos, as I mentioned to Mr. Porter a couple of days ago. Spare embryos are embryos that have been generated in efforts to carry out in vitro fertilization for infertile couples, who number over 2 million in this country.

There's a great deal of interest and activity in the private sector to generate embryos in vitro for the purpose of meeting the hopes of infertile couples. When embryos are generated for therapeutic purposes, and are not used for such purposes, and when proper informed consent is supplied by the individuals who supplied the gametes, the eggs and sperm, it is possible under current law and under the executive order for NIH to consider research with those so-called spare embryos.

We have not as yet funded any research of that sort. Eight grant applications which propose to carry out research of that kind have been approved for funding. But as yet, we have not permitted any of those investigators to carry out research of that kind.

I am in the process of assembling the recommended standing panel that would review the recommendations by our advisory group, consider efforts in public education before we embark on research of this sensitive nature, and advise me about the appropriateness of allowing the investigators, who are responsible for those eight grants, to proceed with research that would involve so-called spare embryos.

Mr. ISTOOK. Let me ask a couple of things in follow-up, and I appreciate the extent of your comment, I really do. If I understand correctly, at this stage no projects have been funded which would have been restricted prior to the 1993 Reauthorization Act?

Dr. VARMUS. That's correct.

Mr. ISTOOK. But you do have eight projects that, if I understood you correctly, have been approved for funding but have not yet been funded.

Dr. VARMUS. No, let me clarify one point, Mr. Istook. Those projects have been funded because the grant applications entail a number of experiments that do not involve the use of pre-implementation human embryos. So other aspects of those grant proposals are being pursued with funds supplied by NIH.

Mr. ISTOOK. All right, so the eight projects have been funded. However, they currently have a restriction upon those eight projects of not doing human embryo research, whether it be with petri dish fertilization or spare embryos or whatever.

Dr. VARMUS. No. These applications do not propose to generate embryos for research purposes.

Mr. ISTOOK. Right. But they would, you currently had a restriction on it, but you're in the process of considering whether to lift that restriction to enable them to do the research with what you call spare embryos?

Dr. VARMUS. That's correct.

Mr. ISTOOK. Okay. And what is the time frame on whether you will make that decision and provide that approval?

Dr. VARMUS. I expect during the course of the next few months to have assembled a group that will provide me with ongoing advice in this area. I expect the panel to consider a number of issues. First of all, I will ask them to review all of what's happened in the last six months, and to look carefully at the deliberations of the earlier advisory groups. I will also ask them to consider ways in which we can better educate the public about this research.

We're very sensitive to the concerns of the public about such research. I don't think we've done an optimal job in educating the public about the nature of the research or its potential enormous benefits. And we need to rectify that. We've made some progress in doing so in the last few months, but I believe we have a fair way to go.

Then we need to ask the assembled panel to consider each of the eight applications individually, and to look at the nature of the research that's being done and to evaluate whether or not it's appropriate to proceed with each. I would expect within the next year we would have some progress on that front.

Mr. ISTOOK. Had it not been for the Presidential directive which limited you to the spare embryos, as you call them, rather than those that have in vitro fertilization, would you be actively considering projects that had fertilization through the petri dish method?

Dr. VARMUS. Yes, we would. And let me add that the process would be the same. We had committed ourselves on December 1st and 2nd in the meeting of my advisory committee to the establishment of a standing panel that would be advising us about the issues that I mentioned, education of the public and overview of the process.

I want to point out that there are many important benefits to be gained from the study of the fertilization process itself. We are concerned about contraceptive research, we are concerned about improving in vitro methods of fertilization for the 2 million infertile couples in this country, and we believe that research of that kind can only go on through in vitro fertilization studies themselves. But we are forbidden at this point from doing such experiments.

Mr. ISTOOK. Let me ask one other question, then relinquish my time. And it's just a simple, straightforward one.

In the in vitro fertilization process, I recognize as you say you want to then not have the tissue grow any further to the point where it would develop organs or whatever it might be. My question is simply, at what stage do you, rather than getting into a philosophical debate, I'll say, halt the growth of the embryo? Is this a matter of hours? Is it a matter of days? And if so, how many hours, how many days?

Dr. VARMUS. The committee that reported to us said that such research should not go on beyond the 14th day. In practice, it is very difficult to get an embryo that's been established in vitro to grow through more than a half dozen divisions or so.

Mr. ISTOOK. Which is what period of time?

Dr. VARMUS. Perhaps three or four days. Customarily, in carrying out in vitro fertilization for therapeutic purposes, one goes only to the 8 or 16 or 32 cell stage, which occurs over 2 to 4 days. To achieve further growth is virtually impossible with current techniques.

Mr. ISTOOK. Sure, because normally the tissue would not remain alive past the three or four day stage.

Dr. VARMUS. That's right. Duplication of cells will not occur. And it is not until about the 14 day stage that one begins to see the formation of what's called the primitive streak.

Mr. ISTOOK. The primitive what?

Dr. VARMUS. The primitive streak, the laying down of what becomes the precursor to the nervous system. So we're dealing at these very early stages with a disordered aggregate of very primitive cells that teaches a great deal about cell differentiation and cancer and many other things.

Mr. PORTER. Mr. Istook?

Mr. ISTOOK. Thank you, Mr. Chairman.

Mr. PORTER. We're operating on the 15 minute rule here. [Laughter.]

I will continue the discussion, though. Could I ask Dr. Varmus—and we will get back to you, Dr. Collins.

Dr. Varmus, what makes an embryo spare in this process, and secondly, what would happen to that spare embryo if it weren't used for research purposes?

Dr. VARMUS. Let me emphasize first of all that all of these embryos are being generated in the private sector at the moment. Also abroad in served countries in a variety of laboratories. In efforts to achieve the aspirations of infertile couples who want to have children, the usual practice is to obtain as many ova as possible, and to fertilize them in vitro with the prospect of obtaining two to four so-called "healthy looking" embryos for reimplantation to produce children for those couples.

In the course of that process, multiple embryos are going to be generated. Now, the criteria by which one chooses which are so-called healthy embryos and likely to survive transportation and implantation in the womb is somewhat uncertain. This is one of the areas of research that's actually quite important to us, because we would like to increase the current, fairly low success rates, around 15 percent, and to make the psychologically difficult process of in vitro fertilization a more successful one.

But whenever one does this therapeutic procedure, there will be embryos of varying degree of vigor that are generated. Those would be simply discarded, be frozen for potential further use at a later date, or with the agreement of the donating parents, used for research purposes. At the moment, of course, those research purposes are carried out only in the private sector.

Mr. PORTER. Now, could you describe why embryo research is more promising than research on other tissue, and why this is an important area for science to pursue?

Dr. VARMUS. Yes, I can give you a number of reasons. First of all, one of the great problems we face is population explosion, and contraceptive methods have not yet, in my view, achieved their full potential. Pharmaceutical houses are characteristically not excited about pursuing this avenue of research for a variety of legal reasons.

We think it's an important goal for us at NIH to try to contribute to a better understanding of the process of fertilization, both for therapeutic purposes to achieve successful in vitro fertilization and to develop better contraceptive methods. We have much better insight into how the sperm and the egg are joined through our understanding of the biochemistry of molecules on the surface of the sperm and the egg. But of course, we can't study that unless we have permission to proceed with the study of the fertilization process.

The second issue that's of great interest concerns the nature of so-called embryonic stem cells. These cells have the capacity to differentiate into virtually any kind of tissue. All work of this sort proceeds with animal models with considerable vigor throughout the biomedical research enterprise. We know from studies of embryonic stem cells of the mouse that we now have the potential to consider using embryonic stem cells as potential universal donors, for example, for bone marrow transplantation and other kinds of therapeutic maneuvers. But we can't begin to pursue such studies with human materials until we're able to use early stage embryos.

DNA SEQUENCING

Mr. PORTER. Thank you, Dr. Varmus. You didn't realize you were going to get all these questions this morning, did you?

Dr. Collins, the February 10th issue of Science reported what seemed to be a rather dramatic development for the Human Genome Project. Two respected scientists, one from Cambridge, England, and one from St. Louis, believe that the entire human genome can be sequenced by the year 2001 for an investment of $300,000,000 to $400,000,000 without the development of new technology. Do you think their approach is feasible?

Dr. COLLINS. This is an exciting development, and it has been sending reverberations through the genome community for the past several months. The investigators, Dr. Robert Waterston at Washington University, St. Louis and Dr. John Sulston at the Sanger Centre, Cambridge England have up until now been the most productive of all of our grantees in terms of their production of DNA sequence. So these are scientists who are speaking from some considerable experience.

Their prediction is that it should be possible to scale up the same kind of technology which they are now using on the roundworm and apply it to human DNA. They propose a process of reducing somewhat the redundancy of the sequencing, so that you don't run over the same region quite so many times, and end up producing about 99 percent of a sequence, but with some gaps.

Because of these gaps, it's important to say this would not be the ultimate sequence. But it would represent the majority of it, at an accuracy of about 99.9 percent and at a cost of about 10 cents per base pair. They propose that this is imaginable by the year 2001, a full five years ahead of the original schedule.

Now, I must say, not everyone in the scientific community agrees that all the steps in this proposal are realistic. There is the question of where the DNA comes from that will be put into sequencing machines. We have not completely solved that question. So I think this should be viewed as an interesting proposal, but not in any way as a definitely possible scenario. But the fact that these two respected scientists are able to stand up and say, this is how we think it might actually and realistically get done, is certainly a milestone in the history of this project and that has generated a lot of excitement.

In response to this excitement, NCHGR is doing everything we can at the present time to try to stimulate the field of DNA sequencing, and particularly to improve the technology to make this more cost-effective. In the current budget for fiscal year 1996, you will see one of the NIH initiatives is for DNA sequencing technology. We don't want to begin a large-scale human sequencing effort before we have optimized the technology, since that might end up being more expensive.

Therefore, now is the time to make a big push on microscaling approaches to DNA sequencing which we believe hold great potential for reducing the cost even further. After all, every time you reduce the cost of sequencing by one cent per base, that saves you $30,000,000. That's pretty worthwhile.

Mr. PORTER. So you are actively looking into this, and you're putting some resources toward looking into sequencing. If you followed this approach and substituted for mapping, would it shift resources from small labs to large ones that could do "industrial grade" sequencing?

Dr. COLLINS. This is a dilemma that we have been facing all along. It is certainly the case that sequencing benefits from an economy of scale. However, that is not an infinitely beneficial equation. At some point in it's growth, a sequencing lab can become sufficiently large and complex, and further economies may no longer be achievable. We do not yet know at what point that is reached.

I believe that we have a limited budget to do this project, and arguments against doing it in a cost effective fashion are therefore not too compelling. On the other hand, I am troubled about the idea of shrinking the number of institutions and laboratories involved in the Human Genome Project down below a certain point. Some mix of these two considerations may well be necessary.

We will not, however, end up in the situation where the entire Human Genome Project is reduced to just turning the crank and getting the sequence done. There will always be technology development, and that is optimally done by a large number of groups in different labs. Some of these groups can be quite small.

PATENTING ISSUES

Mr. PORTER. Yesterday's Washington Post carried a front page article regarding NIH's successful patent of a gene therapy technique, and its award of the commercial rights of development to a local firm. What significance does this event have, both for the field of gene therapy and in terms of NIH's likely financial gain?

Dr. COLLINS. I am aware of the patent, which was issued to Dr. French Anderson, Dr. Michael Blaese and Dr. Steve Rosenberg, three NIH investigators who were the first to develop what's called ex vivo gene therapy, a procedure where you take cells out of the patient, insert a gene into them, and then reinfuse them. That is the approach taken by these investigators to treat the two little girls with severe immunodeficiency, which many people view as the first successful human gene therapy experiment.

The patent is rather broad in its scope. It stems from a collaborative relationship between the NIH and the company Genetic Therapy, Inc. in Gaithersburg. This collaborative mechanism encourages and supports research, and brings the private sector into a very promising area. So in that regard, it seems to be a good thing.

There have been questions raised about whether this patent is too broad, and there may even be some legal challenges raised against it. I am not in a position to say whether those are appropriate or not. Dr. Varmus has been very involved in this area and perhaps he would like to make a comment.

Mr. PORTER. What about the potential for financial gain?

Dr. VARMUS. Well, as you know, the relationship between GTI and NIH emerged from a so-called CRADA, a cooperative research and development agreement, that was first consummated in 1988, and has gone through a number of iterations over the succeeding years. And as a result of that CRADA arrangement, exclusive rights to a license were given to GTI.

The issue of financial gain, of course, will depend entirely on the degree to which ex vivo gene therapy, as Dr. Collins has just described it, will be used on a large scale in therapeutics. At the moment, NIH has a royalty agreement with the company, and the company will sub-license the procedures to other companies and receive royalties directly from anyone who uses it for therapeutic purposes.

It's very difficult for us to estimate right now how much financial reward will come to NIH, because the procedures at the moment are only experimental. We don't know how successful they will be. In the long run, all of us hope that gene therapy will be possible in what is called an in vivo mode, where the therapy is directly delivered to the patient, as opposed to a more laborious procedure involving removal of cells from the individual, treatment of the cells outside, and return of the cells. That escalates the cost.

So we're hoping that over the long haul there will be much more successful approaches and much more economical approaches to gene therapy.

Mr. PORTER. Perhaps someday NIH may become independent and self-funding, like CPB is going to be. [Laughter.]

TECHNOLOGY TRANSFER

There has been quite a bit of attention recently to efforts by private companies to identify large amounts of genome data. The work of TIGR, The Institute for Genomic Research, and NIH alumnus Craig Venter, is often mentioned. Can you explain what these firms are doing and how it relates to the publicly-funded work of your center?

Dr. COLLINS. Certainly. TIGR, and other companies like Incyte and Amgen, have been sequencing the part of the genome that is expressed, called the cDNA's. The cDNA's are the part of the genome that codes for protein. These companies are basically randomly picking clones from a large collection, determining their sequence, and then keeping them in a database.

It is likely that more than 100,000 such sequences currently exist in databases which private companies have produced. Probably TIGR and its parent company, Human Genome Sciences, Inc., have the largest database, but others also exist. The intent in doing this was to learn something about biology, and particularly to look for potential pharmaceutical products downstream. If they found a gene whose sequence predicted a useful property, like causing cells to grow or not to grow, they would be interested in developing that into a product or treatment.

For a time, the impression was that such sequences of unknown function might be patentable, and that created quite a stir. I think the weight of information now is that these sequences are probably not patentable if they are not associated with some proven function or some diagnostic utility. The fact that they are judged by most people probably not to have patentability has, however, resulted in the somewhat unfortunate situation that such sequence databases are now being kept secret.

These databases are an investment by these companies. They are not anxious to give their investment away. So these databases exist in a format where you can only get access to them if you are willing to sign a legal agreement. The HGS agreement says that the results of future research using these sequences can be licensed exclusively by Human Genome Sciences.

This is no doubt good business practice for the companies, and it probably does have some importance for future development of products. For the Human Genome Project, however, the private nature of those sequences has been a difficulty. While gene sequences are useful as they currently exist in terms of sequence data alone, they would be vastly more useful if they could be placed on the genome map in their proper location. Then an investigator looking for a diabetes gene who knows that it is in a certain 10 million base pair interval would know what genes are already there.

This has been a very thorny problem. Happily, a solution has emerged in the last six months about which many of us are quite pleased and excited. Merck, Sharp and Dohme recently made a decision to fund the sequencing of an equivalent set of cDNA's. They are doing this by funding Dr. Robert Waterston at Washington University—who I mentioned a few minutes ago is the highest throughput DNA sequencer—to produce these sequences and to place them immediately in a public domain database, operated by the National Library of Medicine. This project began about two months ago, and there are 5,000 gene sequences being deposited per week into that database.

So in the course of a year, the majority of the human cDNA sequences, the part of the genome that's expressed, will soon be publicly available. We have already seen now emerge, with some encouragement, a consortium of investigators, including our grantees at Genome Science and Technology Centers at Stanford and MIT, to place those sequences on the map. Now that they're publicly available, there's no reason not to do that.

So what had been an awkward, difficult situation now seems to be moving forward in a very positive way. These developments make it quite likely that more than half of the human genes will be placed in their proper location on the map in the next year and a half.

Mr. PORTER. Mr. Istook.

Mr. ISTOOK. Thank you.

Let me ask, well, of course, I'm wondering, too, the Chairman was talking about the Corporation for Public Broadcasting and its funding and profit potential. At NIH, have you thought about seeing if you can strike a deal, if you can track Barney's genes for him? [Laughter.]

Dr. COLLINS. Maybe another model organism should be added to our list.

Mr. ISTOOK. Well, the thing is, if they figure they could clone Barney, they might be able to accelerate their profits and pay you for that.

Dr. COLLINS. We haven't tried that yet.

DEFINITIONS OF SEQUENCING AND MAPPING

Mr. ISTOOK. You were talking about, in reference to the Science magazine article the Chairman mentioned, sequencing versus mapping. What is actually the difference between sequencing and mapping?

Dr. COLLINS. Certainly. It's very much analogous to what an explorer would do when trying to determine the geography of a previously undiscovered part of the world. Columbus had to do this, too. The mapping is the cruder level of information. The maps are the contours of the genome with identifiable milestones placed along each chromosome that tell us roughly where things are. But the sequence is the detailed and complete information, every single A, C, G, and T.

If you've driven down Route 1 from Miami to Key West, you have this long strand of highway going down the Florida Keys. By analogy, the markers on a genetic map are the milestones on that road coming at regular intervals. It's helpful if you're looking for a restaurant, to know that it's near mile marker 84. Similarly, if you are looking for a disease gene, it helps a lot to know what genetic marker it lies close to.

Mr. ISTOOK. Right.

Dr. COLLINS. On the other hand, if you really want to understand how the road was built and all of its properties, the mile markers probably are not going to do it. You need to know much more about the details. That's what the sequence is about. The sequence therefore is more detailed and more difficult.

INTELLECTUAL PROPERTY

Mr. ISTOOK. Certainly. According to this article the Chairman alluded to, they say they can actually accomplish the sequencing for less money in a shorter time, which obviously is a fascinating prospect if it can be done.

Regarding the contract on gene therapy, you mentioned three individuals as NIH researchers receiving the patent. Are the applicable patents actually held by NIH, or are they held by the researchers individually? Who owns the intellectual property right?

Dr. VARMUS. We own the intellectual property.

Mr. ISTOOK. Okay, so in reference to the three researchers receiving the patent, they received it as agents for NIH?

Dr. VARMUS. When that patent was filed, they were all at NIH. Dr. French Anderson, who is one of the three, is now an employee of the University of Southern California.

Mr. ISTOOK. Okay. But the patent's owned by NIH?

Dr. VARMUS. That's correct.

Mr. ISTOOK. That's the crucial point that I want to be sure of.

Dr. VARMUS. Yes, sir.

Mr. ISTOOK. The entity with which you contract, I forget the name of it——

Dr. VARMUS. Genetic Therapy, Inc., that's the company which held the CRADA with us and to which exclusive licensing has been granted.

Mr. ISTOOK. Right. Were any individuals who are now with GTI, were they previously NIH employees as opposed to grantees?

Dr. VARMUS. Yes. One of the, one person who's involved with GTI, I'm not sure exactly in what capacity, is Dr. French Anderson himself. I don't know the composition. The company now has 150 employees, and I don't know how many of them were at one time NIH employees. We could find that out for you.

Mr. ISTOOK. Sure. Yes. I would simply be appreciative of receiving more information, and I realize this is a research environment. But I would just like to know the relationship between the people that are either employed with or doing other work on behalf of the company or who own the company and what their relationship, their historical relationship, has been with NIH.

Dr. VARMUS. Fair enough. I should say that when that CRADA was formed, there was extreme sensitivity to potential conflicts of interest. And very careful consideration was given to this issue by the NIH Office of General Counsel.

Mr. ISTOOK. Certainly. And I also recognize that you cannot expect somebody to succeed in something like that if they do not have a history of working in that area, so you would expect to find some interrelationship with NIH. I would just appreciate, as I say, receiving the information that spells out what it was and what the history of the grants with the company or the people, perhaps working for another entity, had been.

And as I understand it, on royalties it's 50–50? Is that what the agreement is?

Dr. VARMUS. That's as I understand it. Now, I've only known about the details here for the patent being issued since two days ago. We were just trying to get all those facts accumulated through our Office of Technology Transfer. We'd be happy to supply you with any information that would be helpful to you.

Mr. ISTOOK. Sure. Relevant information on that would be appreciated. Thank you very much.

Thank you, Mr. Chairman.

[The information follows:]

CRADA WITH GENETIC THERAPY, INC.

Starting in 1989, the NIH and Genetic Therapy, Inc. (GTI) entered into several cooperative research and development agreements (CRADAs) to do joint research in gene therapy. In 1989 a U.S. Patent Application was filed for methods developed under these CRADAs. From 1990 to 1992 several continuation-in-part (amended) patent applications were filed. On March 21, 1995, the U.S. Patent entitled "Gene Therapy" was granted by the U.S. Patent and Trademark Office to the NIH. This patent broadly claims *ex vivo* gene therapy methods.

In 1990 GTI exercised its option under the CRADA for an Exclusive License Agreement to patent applications. The license granted exclusive rights to GTI to commercialize inventions arising from the CRADAs to GTI. The license gave NIH an up-front payment and yearly minimum payments from GTI for these commercialization rights. In addition, the license provides NIH with royalty payments based on the net sales of GTI or a sublicensee of GTI. Under the Federal Technology Transfer Act of 1986, NIH shares a portion of the royalty payments with the NIH inventors.

Lastly, the GTI prospectus lists four individuals as NIH employees prior to their joining GTI.

Mr. PORTER. Dr. Collins, that's all the questions we have for you. We have others for the record.

We very much appreciate your coming to testify this morning. I think I'm almost as excited about the Center and the project as you are, the wonderful work that you're doing. And as I said, we want to be supportive of it and ensure that it continues to be ahead of schedule and under budget.

Thank you so much.

Dr. COLLINS. Thank you, Mr. Porter.

[The following questions were submitted to be answered for the record:]

DEPARTMENT OF ENERGY ROLE IN THE HUMAN GENOME PROJECT

Mr. Porter: Can your review for us the Department of Energy's continuing role in the human genome project? Has their funding kept pace with the levels originally envisioned in the plan?

Dr. Collins: Since its inception, the Department of Energy's (DOE) role in the Human Genome Project has stressed physical mapping, DNA sequencing, the development of resources, technologies, and instrumentation, the development of computational and database tools, and some work with model systems (particularly the mouse) towards elucidation of human genetic organization.

More recently, studies of ethical, legal and social implications focused on privacy and education issues have been initiated as well. Researchers at the Lawrence Livermore and Los Alamos National Laboratories have developed very high resolution physical maps of human chromosomes 19 and 16, respectively. DOE is the principal supporter of the Genome Data Base at Johns Hopkins, the major database for genome mapping information. DOE also supports the Genome Sequence Data Base in Santa Fe, a major genome sequence database with associated tools for high volume sequence analysis.

As is true of the NIH genome program, the DOE program is shifting additional resources to sequencing with particular emphasis on areas of the genome for which high resolution maps are available. There are several large programs which are jointly supported by the two agencies, for example, the jointly supported Drosophila sequencing project at Lawrence Berkeley Laboratory and the University of California at Berkeley.

The DOE's program funding has not kept pace with the level of support originally envisioned. FY 1995 program funding is $71.9 million per year. An additional $15.8 million of construction funding for the Human Genome Center at Lawrence Berkeley is included in the DOE budget for a total of $87.7 million.

Mr. Porter: Does the Energy Department do its genome work in-house or through extramural grants?

Dr. Collins: The DOE Genome Program supports genome research both at the National Laboratories and at universities (and a small number of private companies). Approximately half of the DOE Genome budget goes to research groups at 8 National Laboratories (Pacific Northwest Laboratory, Lawrence Berkeley Laboratory, Lawrence Livermore National Laboratory, Los Alamos National Laboratory, Ames Laboratory, Oak Ridge National Laboratory, Argonne National Laboratory, and Brookhaven National Laboratory). More than 50 universities are conducting extramural research supported by grants from the DOE Genome Project.

NCHGR STAFFING LEVELS

Mr. Porter: Do you feel your Center is now at full strength with regard to staffing, or do you expect further expansions in later years?

Dr. Collins: The Center is projected to have a level FTE ceiling through the year 2000. Because we were under a hiring freeze, we have not been able to hire all of the staff required to bring us to full strength. Since the freeze has been lifted, we are recruiting in several crucial areas within the Intramural Program, including Medical Ethics, Quantitative Genetics and research on complex genetic diseases, such as, cancer and diabetes. Hiring additional personnel in these areas is essential to carrying out the mission of the NCHGR Intramural Program. It is possible that a few additional FTEs will be required in future years, to fully staff these areas.

GENETIC COUNSELORS TRAINING PROGRAM

Mr. Porter: Tell us more about the "genetics counselors" training program you are initiating. Are scientists or medical practitioners your target population for this training?

Dr. Collins: The Medical Genetics Branch of the National Center for Human Genome Research (NCHGR), and the Department of Health Policy and Management of the Johns Hopkins School of Hygiene and Public Health have developed a unique genetic counseling graduate program. This collaboration brings together resources from the two institutions to address needs in the field. The goals of the new program are to prepare graduates to:

1. provide genetic counseling, with an emphasis on clients' psychological and educational needs;

2. conduct research in the field of genetic counseling; and

3. educate health care providers, policy makers and the public about genetics and related health and social issues.

The impetus for the development of this program is the need for master's level counselors more adequately prepared to conduct therapy for concerns related to genetic conditions, the need for genetic counseling researchers, and the need for advanced training for counselors in health education and program evaluation.

The program will produce a cadre of counselors who will broaden the scope of genetic counseling by generating a research literature that critically examines a variety of aspects of the profession. This academic endeavor will shape future directions in the field. The first students will be admitted in the Fall, 1995.

TECHNOLOGY TRANSFER

Mr. Porter: Despite what we occasionally hear about the problems in transferring technology from NIH to the private market, isn't this an example of successful public-private cooperation?

Dr. Collins: Yes, this patent issued to Genetic Technology, Inc for work done under a Cooperative Research and Development Agreement (CRADA) with NIH, is just one example of many that we have at the NIH, with several in the National Center for Human Genome Research in particular. It is also an example of the Federal Technology Transfer Act working as it was intended.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

Mr. Stokes: While recent scientific discoveries, may prove to be exciting they may also prove to seriously impact citizens on other fronts, especially if research advances out paces ethical, legal, and privacy concerns. For example, recent isolation of a breast cancer gene may warn a woman that she has as much as an 85 percent chance of getting the disease. Such information if not adequately protected could result in employment and insurance discrimination. This is but one example. As we approach fuller utilization of the information stemming from human genome research, to what extent and where possible are we striving to address the ethical, legal, and social issues, and implications before they become major problems?

Dr. Collins: From the inception of the Human Genome Project, it was clearly recognized that acquisition and use of genetic knowledge would have momentous implications for both individuals and society. Analyses of the ethical, legal, and social implications of the potentially widespread availability of genetic information about individuals have been the focus of the initial phase of the NCHGR's ethical, legal, and social implications (ELSI) program. These studies have provided the information necessary for the development of policy options. In FY 1996, the focus will strongly emphasize policy analysis as well as a continuation of research studies.

The issue of dealing with employment discrimination based on genetic information appears to be addressed by the Americans with Disabilities Act (ADA). The EEOC recently issued its formal definition of disabilities as it applies to the ADA. This definition makes it very clear that individuals who have a genetic predisposition to illness, but are currently well, are covered by the ADA.

The states have taken up this issue as well. In the past three years, at least seven states have recognized the potential for discrimination. At the forefront is Wisconsin, which prohibits health insurers from requiring genetic tests and forbids employers from demanding that job applicants undergo such screening. Iowa, Oregon, and Rhode Island passed similar rules covering only employers. California and Ohio enacted new laws last year concerning health insurance, but allowed companies to ask for genetic tests when deciding on coverage for disability or life insurance. Florida has passed laws outlining requirements for informed consent on genetic testing. Lastly, many more states have legislation offering protections for carrier status.

The problem of discrimination in health insurance is not solved. A task force on genetic information and health insurance convened by NCHGR issued its report in May 1993. This report has been made available to legislators and other parties interested in promoting legislation on the state or federal level to protect individuals from discrimination in health insurance.

OUTREACH

Mr. Stokes: Outreach is absolutely essential to the success of and to ensuring that the benefits of human genome research are maximized. How much is included in the FY 1996 budget request for outreach, and how does this compare with the FY 1995 and FY 1994 funding level?

Dr. Collins: Included in the FY 1996 budget request for the National Center for Human Genome Research is $2,407,000 to support outreach activities. The FY 1995 and FY 1994 funding levels for outreach support are $2,324,000 and $1,708,000, respectively. In addition to the outreach program, the NCHGR information office coordinates the publication of literature and the production of videos about The Human Genome Project for dissemination to the public.

COLLABORATIONS

Mr. Stokes: Describe the collaborative relationship that the center has with the Institutes?

Dr. Collins: NCHGR intramural scientists have established over 56 collaborative research projects with scientists at 13 NIH institutes. Examples of collaborative research projects which may eventually permit gene therapy for life threatening illnesses include research on HIV-1 gene therapy with NCI, NHLBI, and NIAID, and cystic fibrosis gene therapy with NIDDK. NCHGR investigators also collaborate on important studies of the genetics of leukemia with NHLBI, and studies of non-Hodgkins lymphoma, melanoma, and BRCA1 currently are underway with NCI scientists. Other institutes involved in NCHGR collaborations include NIAMS, NIDR, NICHD, NEI, NIMH, NINDS, NINR, NIEHS, and the NIH Clinical Center.

MOUSE MAP

Mr. Stokes: The congressional justification also indicates that the Center has essentially completed the genetic map of the mouse. The justification indicates that the mouse map will be an efficient tool for identifying genes responsible for disorders in the mouse. What are the implications of the achievement in its current state for furthering advances in the study of hypertension? Alzheimer's Disease?

Dr. Collins: Hypertension is probably caused by the interaction of several genes and the rat has been shown to be a more appropriate model for hypertension. The mouse genome project has developed the technology for generating genome-wide maps and has shown that this approach is rapid, extremely efficient and cost effective. The efficiency of this technology is now being applied to the development of a rat genome map which will be funded before the end of the fiscal year under the aegis of a multi-institute effort led by NHLBI.

With respect to Alzheimer's Disease, a dense genetic map will facilitate the search for gene(s) contributing to or responsible for Alzheimer's Disease or its homologous condition in the mouse. The recent development of a mouse model of Alzheimer's disease is an excellent example of the power of working with model organisms to understand human illnesses.

APPLICATION OF KNOWLEDGE

Mr. Stokes: While work continues on the physical mapping, even in its current unfinished state, how are the results and knowledge gained thus far being used to further advances and improvements in the diagnosis, treatment and prevention of disease and disorders such as cancer, heart disease, AIDS and sickle disease?

Dr. Collins: A genetic component is now recognized to play a role in almost all human disease and medical conditions, with the possible exception of trauma. Understanding the underlying genetics is becoming a major research approach to developing the capability to design therapeutic and/or preventative measures for dealing with disease. This is particularly true in the case of complex diseases in which both genetic and environmental factors play crucial roles such as cancer and heart disease.

The more rapidly disease genes can be found using the material and informational resources being generated by the Human Genome Project, the more quickly further research will lead to advances and improvements in their diagnosis, treatment and prevention.

With the completion of the human genetic map and with the increasing sophistication of the physical map of the human genome, new disease genes are being found at a rate of several per month compared to a few genes per year not so long ago. For example, genomic resources have played important roles in the identification of the genes responsible for several different cancers, including familial breast cancer, familial colon cancer, and a number of spontaneous leukemias and lymphomas.

It is becoming increasingly clear that a number of genes and/or environmental factors, acting in concert, contribute to an individual's expression of a particular disease. Among the important questions that medical science hopes to answer is why some people exposed to the deadly virus that causes AIDS become ill, while others remain healthy, with no or few outward signs that they are infected.

Similarly, some people who carry a double dose of the gene for Sickle Cell Anemia have severely disabling symptoms, while others function quite well. Animal studies, as well as family, adoption and twin studies of human beings, suggest that modifier genes alone, or modifier genes along with differences in the environment, may play an important role in determining the clinical expression of disease.

Our understanding, and eventual conquest of these diseases, which include not only AIDS and Sickle Cell Anemia, but many forms of cancer and heart disease, is enhanced through the continued efforts of the Human Genome Project to map the human genome and thus help identify these modifiers in addition to the major disease genes that affect the nation's health.

While there is much more to be learned (e.g., what are the clinical consequences of a particular genetic variation? what is the prognostic value of such information?) before such information can be regularly used in the clinical setting, ultimately the information that comes from knowing what the gene is will be very useful. It will allow the development of genetic tests that individuals can use to learn about their genetic predisposition to diseases such as cancer, about means to prevent or delay the onset of disease, and about better ways to treat disease if and when it does develop.

NATIONAL RESOURCE

Mr. Stokes: As the Center provides readily available cloned DNA for gene hunters, the center functions as a national resource. Does the demand for this resource exceed the center's capabilities and capacity?

Dr. Collins: The resources generated by the genome program, including cloned DNA for gene hunters, are available through NCHGR-supported laboratories throughout the U.S. The NCHGR has established a set of research centers, called GESTECs (Genome Science and Technology Centers), that are the primary sites generating the large amount of data emanating from the project. These centers are obliged to release the data and resources to the public within 6 months of finding or developing them. Data are made available through public databases, as well as by public access to the GESTEC's computer server.

Material resources, such as DNA clones, are more difficult for individual laboratories to provide to the general scientific community because of the cost of storing and shipping them. However, this is a very appropriate activity for the private sector. Accordingly, a number of new biotechnology companies have begun to provide genomic resources, such as the DNA clones, and other services, such as helping investigators to identify clones that may be of interest to them. These commercial services are relatively inexpensive, and have begun to play an important role in the genome project by making genome resources available without the need for additional government funds. Without these private enterprises, the existing GESTECs would find it difficult to provide such services to the entire scientific community.

BREAST CANCER

Mr. Stokes: What role did the Center play in the finding of the BRCA1 gene that is implicated in hereditary breast cancer?

Dr. Collins: The NCHGR intramural investigators, along with their collaborators, helped narrow the interval in which the BRCA1 gene was thought be located. Along with the other groups worldwide, we were then able to identify the BRCA1 gene's location in a particular chromosomal region. This allowed researchers to start a focused search for the gene. Investigators at the University of Utah, in collaboration with the National Institute of Environmental Health Sciences and Myriad Genetics, were then able to actually locate the gene. After this group pinpointed the suspect gene, NCHGR intramural scientists were able to verify it was the correct gene by demonstrating that families with inherited breast cancer carried a specific mutation in this gene.

Mr. Stokes: I understand that researchers have found over 40 different mutations in the BRCA1 gene, and each is apparently associated with a dramatically increased risk of breast cancer and/or ovarian cancer. With this valuable knowledge and skill in hand where do we go from here, and how will this knowledge aid in accelerating the race for a cure for breast disease?

Dr. Collins: The existence of many mutations in this gene tells us that it plays an important role in the development of breast cancer. NCHGR intramural scientists and others have proven that inheriting a defective copy of this gene leads to an almost sevenfold increase in the risk of breast cancer--up to 85 percent risk. The challenge that lies ahead is to determine the biological function of this gene. It is necessary to be able to understand how and when tumors start to develop. This will also allow these scientists to determine if the BRCA1 gene plays a role in all breast cancers or just a subset of the 186,000 cases diagnosed yearly. In the best case scenario, our work in the NCHGR intramural program will enable us to completely understand why having a defective copy of a BRCA1 gene causes a normal cell to transform into a tumor. Using this knowledge scientists could then design a drug that restores or replaces the function of the defective gene thereby stopping the tumors before they get a chance to start.

Although it will take many years to know whether or not the above scenario will come true, the isolation of this gene will have immediate benefit to those in "high risk" families who can be tested as part of research protocols for the presence of BRCA1 mutations. Research going on at NCHGR right now involves the genetic and medical counseling of individuals from these high risk families.

PROSTATE CANCER

Mr. Stokes: Are we getting closer to identifying the genes implicated in prostate cancer?

Dr. Collins: The NCHGR intramural scientists are now in the midst of genotyping 300 individuals from families predisposed to hereditary prostate cancer. These families were collected over many years at Johns Hopkins University. To date, they have covered approximately 13 percent of the genome for these individuals. More families are being collected for the study as well as to improve the statistical power of the analysis. Our goal is to identify the location of a gene(s) that strongly predisposes 1 in 200 U.S. males to prostate cancer.

RESEARCH GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the congressional justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your institute, what has been the trend in success rate over the past five years?

Dr. Collins: The trend in success rates for NCHGR over the past five years is as follows:

FY 1992 - 22%
FY 1993 - 28%
FY 1994 - 28%
FY 1995 - 19% (est.)
FY 1996 - 25% (est.)

Mr. Stokes: What has been the trend in the average cost of research grants over that same time period? What is the trend in terms of constant dollars?

Dr. Collins: The trend in average cost for all RPGs for NCHGR over the past five years in current dollars and constant dollars, using FY 1992 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, is as follows:

Year	Current Dollars	Constant Dollars
FY 1992	$342,900	$342,900
FY 1993	$380,000	$364,700
FY 1994	$444,100	$409,100
FY 1995	$469,800	$415,600
FY 1996	$542,400	$460,900

Mr. Stokes: What is the success rate for research applications received from minority researchers? from women? from African Americans? from HBCUs?

Dr. Collins: In FY 1994 the NCHGR received a total of 199 research grant applications. Of the 15 minority applicants who responded to the optional question on the grant application regarding race, three received funding. This translates to a success rate of 20 percent. Fifty three of the grant applicants did not respond to the optional question regarding race and were placed in the unknown category. Since there is no way to predict the composition of the applicants in the "unknown" category, the data may not provide a true representation of NIH's support of minority researchers.

The NCHGR received 54 applications from women researchers in FY 1994. Twelve of these applications received funding for a success rate of 22 percent. Data on gender of applicants was not available for nine applications in FY 1994.

Of the applicants who responded to the optional question on race, none were identified as African American applicants. One application from an HBCU was received in FY 1994. This application was not funded.

The NCHGR did receive three requests from minority researchers for research supplements to RCMI grants. All three requests were from HBCUs and one of the requests was from an African American female. All three of these supplements were funded.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women? to minority researchers? to African American researchers? to HBCUs?

Dr. Collins: Average cost data for all RPGs for minority, women, and African American researchers for the period of FY 1992 through FY 1994, using FY 1992 as the base and the BRDPI as the inflation index, is as follows:

Year	Current Dollars	Constant Dollars
FY 1992		
Women	$307,000	$307,000
Minorities	N/A	N/A
African Americans	N/A	N/A
HBCUs	N/A	N/A
FY 1993		
Women	$301,500	$289,380
Minorities	$396,512	$380,572
African Americans	N/A	N/A
HBCUs	N/A	N/A
FY 1994		
Women	$256,100	$235,919
Minorities	$147,391	$135,777
African Americans	N/A	N/A
HBCUs	N/A	N/A

Again, in FY 1994 53 applicants did not respond to the optional question on the application regarding race. The number of applicants who did not respond to this question in FY 1993 and FY 1992 was 17 and 44, respectively.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

FY 1996 Budget — Page No.

Organization chart........ 2

Appropriation language........ 3

Amounts available for obligation........ 5

Budget mechanism table........ 6

Summary of changes........ 8

Budget authority by object........ 10

Administrative costs........ 12

Authorizing legislation........ 13

Appropriation history........ 14

Budget authority by activity........ 15

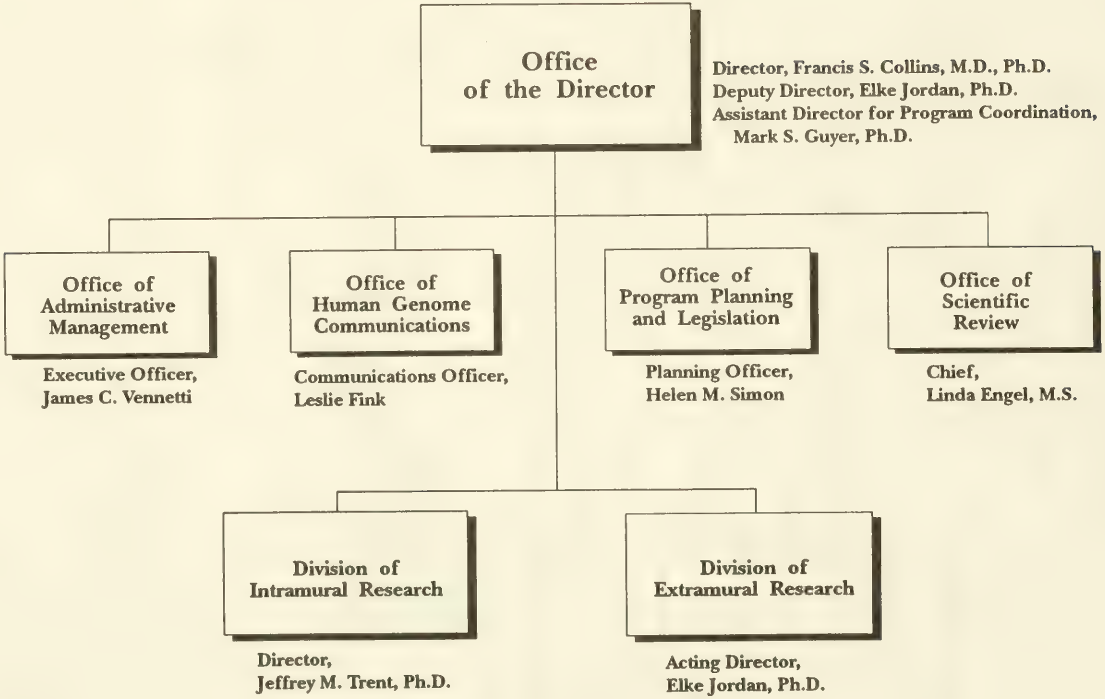
Justification:

A. General statement........ 17
B. Extramural research........ 21
C. Intramural research........ 28
D. Research management and support........ 32
E. Detail of full-time equivalent employment (FTE)........ 33
F. Detail of end-of-year employment........ 34

2

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Organizational Structure



Office of the Director

Director, Francis S. Collins, M.D., Ph.D.
Deputy Director, Elke Jordan, Ph.D.
Assistant Director for Program Coordination,
Mark S. Guyer, Ph.D.

Office of Administrative Management

Executive Officer,
James C. Vennetti

Office of Human Genome Communications

Communications Officer,
Leslie Fink

Office of Program Planning and Legislation

Planning Officer,
Helen M. Simon

Office of Scientific Review

Chief,
Linda Engel, M.S.

Division of Intramural Research

Director,
Jeffrey M. Trent, Ph.D.

Division of Extramural Research

Acting Director,
Elke Jordan, Ph.D.

1/9/95

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

For carrying out section 301 and Title IV of the Public Health Service Act with respect to human genome research, [$152,010,000] $166,678,000.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Center For Human Genome Research

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$128,701,000	$152,010,000	$166,678,000
Rescission in accordance with PL 103-211..............	-1,589,000		
Section 205 Procurement reduction....................		-136,000	
Section 513 S&E reduction.......		-25,000	
Subtotal, Adjusted Appropriation................	127,112,000	151,849,000	166,678,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities......	-637,000		
Comparative transfer from: Other NIH Institutes for Management Fund adjustment....		17,000	
Subtotal, adjusted budget authority...........	126,475,000	151,866,000	166,678,000
Unobligated balance, lapsing	-95,000		
Total obligations...........	126,380,000	151,866,000	166,678,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994--$554,000; FY 1995--$2,200,000; FY 1996--$2,350,000.

Also excludes funding for HIV activities: FY 1995--$1,000,000; FY 1996--$1,000,000, included in Office of AIDS Research, NIH.

Note: Excludes $11,041 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	77	$37,312,000	94	$47,142,000	82	$48,468,000
Admin. supplements	(5)	498,000	(4)	467,000	(4)	487,000
Competing:						
Renewal	19	10,912,000	11	4,166,000	12	5,314,000
New	36	9,903,000	22	7,894,000	33	14,615,000
Supplements	0	0	0	0	0	0
Subtotal, competing	55	20,815,000	33	12,060,000	45	19,929,000
Subtotal, res. proj	132	58,625,000	127	59,669,000	127	68,884,000
SBIR/STTR	10	1,553,000	10	2,180,000	9	2,948,000
Total, RPGs	142	60,178,000	137	61,849,000	136	71,832,000
Research centers:						
Specialized/comp. centers	12	32,956,000	14	35,195,000	14	38,447,000
RCMI	(2)	259,000	(2)	280,000	(2)	292,000
Subtotal, centers	12	33,215,000	14	35,475,000	14	38,739,000
Other research:						
Research career programs	12	903,000	12	908,000	12	935,000
Other research related	21	1,180,000	35	2,151,000	35	2,213,000
Subtotal, other research	33	2,083,000	47	3,059,000	47	3,148,000
Total, research grants	187	95,476,000	198	100,383,000	197	113,719,000

Training:						
Individual awards:						
Noncompeting	15	382,000	13	369,000	12	351,000
Admin. supplements	(1)	1,000	0	0	0	0
Competing	11	323,000	4	114,000	5	146,000
Subtotal, individual	26	706,000	17	483,000	17	497,000
Institutional awards:						
Noncompeting	140	3,158,000	13	394,000	93	2,297,000
Competing	0	0	93	2,232,000	13	405,000
Subtotal, institutional	140	3,158,000	106	2,626,000	106	2,702,000
Total, training	166	3,864,000	123	3,109,000	123	3,199,000
Research and development contracts	7	2,130,000	7	2,575,000	5	2,616,000
	FTEs		FTEs		FTEs	
Intramural	80	18,824,000	135	39,389,000	135	40,543,000
Research management and support	59	6,181,000	61	6,410,000	61	6,601,000
Total	139	126,475,000	196	151,866,000	196	166,678,000

8

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Summary of Changes

1995 Estimated budget authority	$151,866,000
1996 Estimated budget authority	166,678,000
Net Change	+14,812,000

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase		$12,420,000		+$113,000
b. Annualization of January 1995 pay raise		12,420,000		+62,000
c. Annualization of January 1995 locality pay		12,420,000		+38,000
e. January 1996 pay increase		12,420,000		+207,000
f. Increased cost of centrally furnished services		4,870,000		+566,000
g. Increase cost of service and supply fund		1,655,000		+48,000
h. Increase cost of supplies and materials		20,444,000		+593,000
Subtotal				+1,627,000
2. Research Management and Support				
a. Within grade increase		3,755,000		+55,000
b. Annualization of January 1995 pay raise		3,755,000		+19,000
c. Annualization of January 1995 locality pay		3,755,000		+11,000
e. January 1996 pay increase		3,755,000		+62,000
f. Decreased cost of centrally furnished services		1,062,000		-10,000
g. Increase cost of service and supply fund		173,000		+5,000
h. Increase cost of supplies and materials		1,420,000		+41,000
Subtotal				+183,000

Summary of Changes (con't)

B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting............	94	47,142,000	-12	+1,326,000
b. Admin supplements.......	(4)	467,000	---	+20,000
c. Competing...............	33	12,060,000	+12	+7,869,000
d. SBIR/STTR...............	10	2,180,000	-1	+768,000
Total...................	137	61,849,000	-1	+9,983,000
2. Research centers............	14	35,475,000	---	+3,264,000
3. Other research..............	47	3,059,000	---	+89,000
4. Research training...........	123	3,109,000	---	+90,000
5. Research & dev contracts....	7	2,575,000	-2	+41,000
	FTEs	Amount	FTEs	Amount
6. Intramural:				
a. Gene therapy program increase......	135	39,389,000	---	+500,000
b. Program decrease........	135	39,389,000	---	-973,000
7. Research management and support:				
a. DNA sequencing program increase......	61	6,410,000	---	+100,000
b. Program decrease........	61	6,410,000	---	-92,000
Subtotal................				+13,002,000
Total changes...........				+14,812,000

10

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.......	196	196	---
Full-time equivalent of overtime and holiday hours..................	2	2	---
Average ES salary......................	$112,242	$114,094	+$1,852
Average GM\GS grade....................	10.4	10.4	---
Average GM\GS salary...................	$45,971	$47,105	+$1,134
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)...	$36,225	$36,576	+$351
Average salary of ungraded positions....	$52,290	$53,418	+$1,128
Personnel compensation:			
Full-time permanent..................	$6,672,000	$6,976,000	+$304,000
Other than full-time permanent........	2,651,000	2,781,000	+130,000
Other personnel compensation..........	358,000	375,000	+17,000
Special personnel service payments....	4,000,000	4,000,000	---
Subtotal, personnel compensation......	13,681,000	14,132,000	+451,000
Personnel benefits.....................	2,488,000	2,604,000	+116,000
Benefits for former personnel..........	6,000	6,000	---
Travel and transportation of persons....	358,000	368,000	+10,000
Transportation of things...............	309,000	318,000	+9,000
Rent, communications, and utilities.....	418,000	422,000	+4,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Printing and reproduction..............	65,000	67,000	+2,000
Other services:			
Consulting services..................	263,000	271,000	+8,000
Other sevices........................	6,996,000	6,761,000	-235,000
Purchases from government accounts....	10,070,000	10,727,000	+657,000
R&D contracts........................	2,575,000	2,616,000	+41,000
Supplies and materials.................	7,433,000	7,648,000	+215,000
Equipment..............................	3,683,000	3,790,000	+107,000
Grants, subsidies & contributions.......	103,492,000	116,918,000	+13,426,000
Insurance claims and indemnities........	29,000	30,000	+1,000
Total...............................	151,866,000	166,678,000	+14,812,000

12

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)	$6,672,000	$6,976,000	+$304,000
Other than Full-time permanent (11.3)	2,651,000	2,781,000	+130,000
Other Personnel Compensation (11.5)	358,000	375,000	+17,000
Special Personnel Service (11.8)	4,000,000	4,000,000	0
Total Personnel Compensation (11.9)	13,681,000	14,132,000	+451,000
Personnel Benefits (12.0)	2,488,000	2,604,000	+116,000
Benefits for Former Personnel (13.0)	6,000	6,000	0
Travel (21.0)	358,000	368,000	+10,000
Transportation of Things (22.0)	309,000	318,000	+9,000
Rental Payments to Others (23.2)	42,000	43,000	+1,000
Communications, Utilities, and Miscellaneous Charges (23.3)	376,000	379,000	+3,000
Printing and Reproduction (24.0)	65,000	67,000	+2,000
Consulting Services (25.1)	263,000	271,000	+8,000
Other Services (25.2)	6,996,000	6,761,000	-235,000
Purchase of goods and services from government accounts (25.3)	9,609,000	10,266,000	+657,000
Supplies and materials (26.0)	7,426,000	7,640,000	+214,000
Total	41,619,000	42,855,000	+1,236,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation..	Section 301	42s241	Indefinite	$148,757,000	Indefinite	$163,479,000
National Center for Human Genome Research	Section 485B	42s285g	Such sums as necessary		Such sums as necessary	
National Research Service Awards	Section 487(d)	42s288	Such sums as necessary	3,109,000	Such sums as necessary	3,199,000
Total Budget Authority....				151,866,000		166,678,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1990	$100,000,000	$62,000,000	---[2]	$59,938,000
1990 Sequester				-400,000
1991	108,029,000	66,131,000	108,264,000	87,418,000[3]
1991 Sequester				-1,000
1992	110,487,000	93,115,000	109,309,000	104,762,000[4]
1993	110,429,000	107,217,000	107,217,000	106,239,000[5]
1994	134,549,000	119,030,000	131,925,000	127,112,000[6]
1995[7]	152,010,000	151,878,000	151,878,000	151,849,000[8]
1996[7]	166,678,000			

[1] Reflects enacted supplements, rescission, and reappropriations.

[2] The Senate did not provide funds for the National Center for Human Genome Research; however, the Senate allowance included $61,847,000 for the Human Genome Initiative within the National Institute of General Medical Sciences' account.

[3] Excludes enacted administrative reductions of $2,313,000 and the enacted rescission of $116,000.

[4] Excludes enacted administrative reductions of $383,000.

[5] Excludes enacted administrative reductions of $978,000.

[6] Excludes rescission of $1,589,000.

[7] Excludes funds for HIV research activities consolidated in the NIH Office of AIDS research in FY 1995 and FY 1996.

[8] Excludes enacted administrative reductions of $136,000 and $25,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Human Genome Research...		$99,836		$100,517		$101,470		$106,067		$119,534		+$13,467
Intramural Research.....					80	18,763	135	39,389	135	40,543	---	+1,154
Research mangement and support...........	44	4,920	55	5,578	59	6,147	61	6,410	61	6,601	---	+191
Total obligations.....	44	104,756	55	106,095	139	126,380	196	151,866	196	166,678	---	+14,812
Unobligated balance lapsing...............		6		39		95						
Total, budget authority.	44	104,762	55	106,134	139	126,475	196	151,866	196	166,678	---	+14,812

15

Justification

National Center for Human Genome Research

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
139	$126,475,000	196	$151,866,000	196	$166,678,000	---	+$14,812,000

General Statement

As FY 1996 begins and we come to the end of the first 5-year planning period for the Human Genome Project, we can see great progress according to the measuring stick we established for ourselves at the start. The accomplishments of those first 5 years have positioned us so that the end goal is now in sight. Obtaining the complete sequence of human DNA by 2005, still offers large and complex technological problems, but the path to it is now much clearer. The next major phase of the Human Genome Project, beginning in FY 1996, promises to be an exciting new era for genetics.

In FY 1994 we reached the first goal of the Human Genome Project (HGP), with the publication of an integrated human genetic linkage map that was even better than the one envisioned at the beginning of the HGP. The FY 1996 request includes funds that will bring us close to the next goal, physical mapping, and an increase in our investment in developing technologies for rapid, low-cost DNA sequencing.

The physical mapping effort is progressing well, with about one-half of the number of markers necessary from the human genome now publicly available in computer databases. Arrays of overlapping, ordered DNA clones--physical maps, for several human chromosomes are 70 to 90 percent complete. Some of these maps cover as many as 50 million base pairs of continuous chromosomal DNA and provide readily available cloned DNA for gene hunters. Over the next few years, we will continue to improve the resolution of physical maps, increasing the value of these maps in searching for disease genes.

Our investment in developing technologies for rapid low-cost DNA sequencing has already led to much-improved methods to begin to take on large-scale DNA sequencing. Nearly 10 million bases of DNA from the genome of the roundworm, C. elegans, have been sequenced in technology development studies. Several other research groups have each succeeded in sequencing 500,000 to 1,000,000 bases of DNA with existing technologies. Further increases in the speed and efficiency of DNA sequencing are anticipated from the application of miniaturization technologies to sequencing and integration and modularization of process components. To stimulate the development of this technology, the NCHGR has increased the investment in this area in FY 1995 and a further increase is requested for FY 1996. Every reduction of $0.01 per base pair in the incremental cost of sequencing results in a $30 million savings in the total cost of sequencing the human genome. Thus, it is anticipated that the cost savings achieved by stimulating the rapid development of these technologies will more than justify the investment.

Accomplishing the current goals in the next few years will provide the research community with a growing resource for finding genes in human DNA, as well as in the DNA of several important model organisms. Already genome maps have led to the isolation of important disease genes such as the p16 gene, a gene implicated in familial melanoma, and most notably the BRCA1 gene for hereditary breast cancer. Again, examination at the DNA level has revealed interesting biology. Researchers have already found over 40 different mutations in the BRCA1 gene, each apparently associated with a dramatically increased risk of breast cancer and/or ovarian cancer.

Scientists in the Division of Intramural Research have begun applying these genome resources and developing new technologies to study the fundamental mechanisms of inherited and acquired genetic disorders, thereby combining the forces of technology and biology to solve the problems of human genetic disease. These intramural researchers have begun to unravel the complexities of psychiatric illnesses, cancers, diabetes, and skeletal and metabolic disorders and are developing new DNA-based methods for diagnosis and treatment of genetic disorders.

From the inception of the HGP, it was clearly recognized that acquisition and use of such genetic knowledge would have momentous implications for both individuals and society. Research studies and analyses of the ethical, legal, and social implications (ELSI) of to the potentially widespread availability of genetic information about individuals have been the focus of the initial phase of the ELSI program. These studies have provided the information necessary for analysis of policy options. In FY 1996, the focus will strongly emphasize policy analysis as well as a continuation of research studies.

In line with this approach, NCHGR, in collaboration with other NIH Institutes, launched a major initiative to study a variety of questions about the delivery of genetic tests for cancer predisposition. With genes predisposing to cancer being discovered at an increasing rate, information from this set of studies will help guide health care professionals, and patients, to use DNA testing technologies responsibly. Because a basic understanding of the principles of heredity and DNA science will help the public make informed health care choices, the ELSI program will also continue to emphasize public education in FY 1996.

The President's appropriation request of $166,678,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Center for Human Genome Research for the past 5 years has been as follows:

Year	Amount	FTE
FY 1991	87,398,000	37
FY 1992	104,762,000	44
FY 1993	106,134,000	55
FY 1994	126,475,000	139
FY 1995	151,866,000	196

Purpose and Method of Operation

The NCHGR carries out its mission through the support of research project grants, research center grants, research career awards, other research grants, training grants and fellowships, and inter-agency agreements with other Federal agencies. In addition, the NCHGR supports an intramural research program which conducts research on genes and their function in the causation of disease and, hopefully, the eventual prevention or cure of human diseases. The scientific and administrative management and other overhead items are funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1996 budget request for the National Center for Human Genome Research is $166,678,000. This amount represents an increase of $14,812,000 or 9.8 percent over the FY 1995 estimate. This budget includes specific increases for NIH special initiative areas, the largest of which is DNA sequencing technology development. NCHGR will play the major role in this NIH initiative. Other, smaller increases have been provided for NIH research initiatives in the areas of brain and brain disorders, mutations and environmental cancer, and gene therapy. In addition, funds were provided for the Administration's initiative for breast cancer research.

The funds requested for the above initiatives will be used to support additional research project grants and increases to current human genome research centers to make maps and develop the methods and technology needed to help scientists find the genes for the various diseases more rapidly. Additionally, NCHGR will be funding more research projects working on new technologies for DNA sequencing. Within the Division of Intramural Research, investigators will be developing gene therapy treatments for different genetic diseases or those with a genetic component.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the non-competing component, average grant awards received a 4 percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. The FY 1996 budget request for non-competing research project grants is $48,468,000, an increase of $1,326,000 or 2.8 percent, for 82 awards as compared to the FY 1995 estimate of $47,142,000 for 94 awards. This budget request includes $19,929,000, an increase $7,869,000 or 65.2 percent, for 45 competing research projects grants as compared to $12,060,000 for 33 awards in the FY 1995 estimate.

The FY 1996 budget request for research centers is $38,739,000, a 9.2 percent increase over FY 1995. The FY 1996 budget request for other research grants is $3,148,000, an increase of $89,000, or 2.9 percent, over FY 1995 for the same number of awards. The FY 1996 budget requests $3,199,000 for research training, an increase of $90,000, or 2.9 percent, for the same number of full-time trainee positions. For research and development contracts and inter-agency agreements, the request is $2,616,000, an increase of $41,000, or 1.6 percent, for 5 awards, as compared to $2,575,000 for 7 awards in FY 1995.

The FY 1996 budget request includes $40,543,000 for the Division of Intramural Research. This is an increase of $1,154,000, or 2.9 percent, over the FY 1995 estimate.

The FY 1996 budget request provides $6,601,000 for research management and support activities, an increase of $191,000, or 3 percent, over the FY 1995 estimate. This increase will provide for basic mandatory increases.

National Center for Human Genome Research

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act.
1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$101,470,000	$106,067,000	$119,534,000	+$13,467,000

The objective of the Human Genome Project is to construct detailed genetic and physical maps of the human genome, to determine the complete sequence of human DNA, to localize the estimated 50-100,000 genes within the human genome, and to perform similar analyses on the genomes of several other organisms that are extensively used in research laboratories as model systems.

Progress to date and future plans for achieving the above goals are described below. Funding for the extramural program of the NCHGR for the last 5 years has been as follows:

Year	Amount
FY 1991	$83,681,000
FY 1992	99,836,000
FY 1993	100,517,000
FY 1994	101,470,000
FY 1995	106,067,000

Rationale for the budget request

The FY 1996 request is $119,534,000, an increase of $13,467,000, or 12.7 percent, over the FY 1995 estimate. Current progress and future plans for attaining the new goals of the Human Genome Project are outlined below.

Genetic Mapping

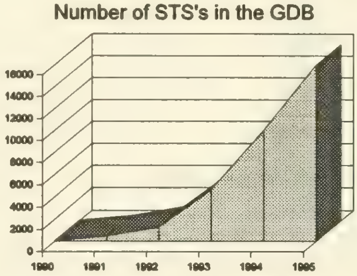
Exceeding the 5-year goal: NCHGR's initial goal of constructing a human genetic map consisting of about 2,000 randomly-spaced markers, was exceeded this year with the construction of an integrated map comprised of over 5,000 markers. An NCHGR-funded group of collaborators centered at the University of Iowa spearheaded this effort, using data contributed by many laboratories, both in the U.S. and abroad.

Mouse genetic map: This map has also been essentially completed by NCHGR-supported investigators, thus achieving another of the original 5-year goals. The mouse is an important research model because many disorders in mouse are similar to those found in humans. The mouse genetic map, which now contains over 5,000 markers, provides a rapid, efficient tool for identifying the genes responsible for disorders in the mouse. Investigators can study how these genes function in the mouse and can use the mouse genes as candidate disease genes in similar human disorders. For example, the discovery of a gene responsible for obesity in the mouse, and a potentially similar gene in the human, relied heavily on the mouse genetic map.

Rat genome--another effective model: A genetic map of the rat would contribute similarly to understanding diseases that are modeled more effectively in the rat than in the mouse. Technologies developed and lessons learned during construction of the human and mouse maps can be applied to lower the cost and shorten the time required for a rat genome mapping project. NCHGR has collaborated with the National Heart, Lung and Blood Institute (NHLBI) by providing technical advice and helping to coordinate the activities of several Institutes of the NIH, leading to the issuance of a Request for Applications by NHLBI to build a rat genetic map. This effort was identified by the Director, NIH, as a priority investment.

Physical Mapping

Meeting the 5-year goal: Construction of the human physical map continues at a rapid pace. A number of NCHGR-supported physical mapping efforts have now each hit a steady state of production. The total number of mapped "sequence tagged sites," (STS--a short DNA sequence that uniquely identifies a mapped gene or other marker) in the publicly accessible Genome Data Base has already reached over 15,000, about one-half of the minimum number needed to reach the physical mapping goal. It is expected that this goal, of at least 30,000 STS markers over the entire genome (an average of one STS every 100,000 base pairs), will not only be met but will be exceeded in the next few years. The rapid pace of production and the effectiveness of NCHGR's policy of rapid release of data to a public database is evident from the increase in the number of STS markers available in the Genome Data Base.



A recent initiative, funded by private industry, will produce a very large number of gene-based markers. The STSs representing these markers will be rapidly incorporated into the physical map by on-going physical mapping efforts funded by NCHGR and international collaborators . It is anticipated, therefore, that the 100,000 base pairs STS map will include a substantial number of genes.

Building better physical maps: During FY 1996, one human genome research center will use a new application of the radiation hybrid (RH) mapping method to produce a map of the entire human genome that will integrate with and confirm the STS maps being built by other human genome research centers. The RH map is very cost-effective and efficient at establishing marker order. The use of more than one method to produce the physical maps will result in more accurate and detailed maps, as the methods complement each other.

Value of physical maps: The usefulness of the maps continues to be reflected in the pace at which new disease genes are being isolated. The increase in the density of STS markers can be expected to further accelerate this pace. The availability of the mapping information through computers and commercially available kits for using the STS markers, have made the products of the HGP widely used in the biological research community.

DNA Sequencing

The technological challenge remains: The most ambitious goal of the Human Genome Project is the determination of the sequence, or order, of the three billion individual nucleotides in human DNA. However, the effort will be worth it as even the modest amount of DNA sequence that has been obtained to date from the genomes of the human and several model organisms has provided a wealth of new information about genes, their structure, expression, and function. Completion of the sequence of the human genome will allow for a much more comprehensive understanding of all human genes. While improvements in DNA sequencing technology have been dramatic, with several steps in the process having been either partially or completely automated, substantial improvements in sequencing technology will still be required to attain the cost efficiency and rate of throughput necessary to make sequencing of the human genome a reality. To ensure the development of this technology, the NCHGR has made a modest investment in this area in FY 1995 and a further increase is being made in FY 1996.

Pushing current technology to increase throughput: The largest amount of DNA sequence to date has been produced by an NCHGR-supported research team in the U.S., in collaboration with a British research group. These groups have as their goal the sequence of the genome of the roundworm C. elegans and together, they have now sequenced approximately 10,000,000 bases, or about 10 percent, of the genome of this important model organism. Through innovative strategies, these investigators have pushed the capacity of the state-of-the-art sequencing technology, such that their rate of sequencing is approximately 11,000,000 bases per year of finished sequence. This compares with their rate of about 2,000,000 bases per year just one year ago. These rates of sequence production allow confidence that the complete DNA of C. elegans will be determined by the end of 1998, as called for in the new 5-year plan and well ahead of initial expectations.

Increase in sequencing rates for human DNA: An extremely encouraging development of the past year is that several groups have each succeeded in sequencing approximately 1,000,000 bases of human DNA. This achievement is an important stepping stone toward the complete sequence of human DNA. It is anticipated that the rates of production for human DNA sequence will continue to increase as improved technology becomes available.

Potential for dramatically improved sequencing technology: Recent advances have demonstrated that dramatically improved DNA sequencing technology can be expected through the application of existing miniaturization and automation technologies to state-of-the-art gel-based electrophoretic genomic sequencing methods. Investigators have obtained data suggesting at least a tenfold increase in sequencing throughput can be achieved using either capillary gels or ultrathin gels. These approaches should also yield a substantial cost savings due to the reduction in sample size. Prototype instruments using these approaches are under development.

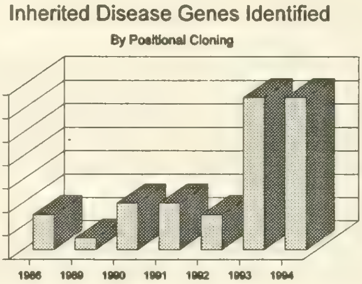
Additional reductions in scale may be anticipated through the application of microfabrication and microelectro mechanical systems (MEMS) technology, originally developed in the semiconductor industry. This technology could increase the speed for sequencing by 2 to 3 orders of magnitude, and cost savings due to reductions in scale could be dramatic. In order to encourage future work in the area of technology development, the NCHGR invested additional funds in this area in FY 1995 and plans a larger investment in FY 1996. This investment could more than pay for itself in cost savings due to increased efficiencies downstream.

Gene Identification

Finding disease genes: The improved genomic maps produced by the HGP have facilitated the mapping of genes responsible for those genetic diseases that are caused by single genes and are absolutely essential for identifying the multiple genes that cause genetically complex diseases. For example, using the most up-to-date maps, five regions of the genome responsible for insulin-dependent diabetes were identified in FY 1994, a major step forward in unravelling the complex genetics of this common human illness. Tracking altered genes in diabetes and other genetically complex diseases remains a daunting task, requiring improved technology to efficiently use the improved maps for genotype analysis of large numbers of individuals. In FY 1996, NCHGR will continue to support research to develop new methods and devices for lower cost, more rapid, and higher throughput for genotype analysis.

Other techniques for finding disease genes: While the generation of genetic and physical maps is expediting the discovery of disease genes by allowing the regions where these genes reside to be delimited and defined more efficiently, finding a gene of interest continues to be formidable. NCHGR supports the development and refinement of biological and computational techniques that facilitate the discovery of genes within a defined region of DNA. Two biological methods, exon trapping and direct cDNA selection, have shown great promise in identifying genes within a defined region of DNA based on specific functional properties. In addition, genes are being found through the computational analysis of DNA sequences and the reliance on this type of approach will grow as more DNA sequenced is obtained.

A number of disease genes have been discovered using these technologies, most notably BRCA1, one of the major genes implicated



in early onset breast and ovarian cancer. This gene was ultimately found using the method of direct cDNA selection; however, many researchers tried a number of different techniques including exon trapping and DNA sequencing to identify genes within the region defined by genetic linkage. An important lesson that was learned from this and other extensive investigations is that no single technique can yet find all of the genes in a piece of DNA. During FY 1996, the NCHGR will continue to support the development of these and other new technologies for gene identification.

Placing genes on the physical map: In addition to developing methods for finding individual genes of interest within specific, relatively small regions of DNA, technology for the placement of genes onto the physical map on a genome-wide scale is also one of the current 5-year goals. The importance of having a large number of mapped genes was reinforced this summer when the gene for achondroplasia was identified. During the long search for the Huntington's Disease (HD) gene, several genes, in addition to the HD gene itself, had been localized in the same region, but their association with any specific disease was not readily apparent. Some time after these genes were identified, the gene for achondroplasia was genetically mapped to the same general chromosomal region. Since several genes were already mapped to this location, there were candidate genes immediately available for study and one was rapidly determined to be the gene for achondroplasia.

Genome Informatics

Computerized databases are the principal means by which the results of the Human Genome Project are disseminated to other genome researchers, the broader biomedical research community, and, increasingly, to medical practitioners. The NCHGR currently supports 4 different databases containing information about the genomes of 3 model organisms--mouse, fruitfly, and yeast--and the human genome. The usefulness of these databases is shown by the rapid increases in the level of usage over the prior year as shown in Table 1.

Table 1 - Genome Database Usage

	December 1994 Level	Increase over prior year
Human World Wide Web queries per week	2,035	502%
Mouse World Wide Web queries per week	4,125	162%
Fruitfly Gopher transactions per week	6,210	149%
Yeast Gopher transactions per week	1,700	387%
Yeast World Wide Web queries per week	3,107	514%

The model organism databases are proving useful both to researchers studying the genetics and biology of these organisms and to researchers studying human disease. For example, the mouse database is routinely queried by molecular biologists who have cloned a gene for a particular function and want to know whether it is the same as any gene previously mapped to the same chromosomal region. The database is also heavily used by researchers to select the best mouse mutant models of human diseases. Recently, the database has been used to find Alzheimer's-related genes in the mouse, to find candidate genes for particular disease-resistant phenotypes, and to locate information useful in studying atherosclerosis.

Ethical, Legal, and Social Implications (ELSI) of Genomic Research

From the inception of the HGP, it was clearly recognized that the acquisition and use of genetic knowledge would have momentous implications for both individuals and society and would pose a number of consequential choices for public and professional deliberation. The NCHGR focuses on 4 major areas of interest--ethical issues surrounding genetics research; the responsible clinical integration of new genetic technologies; privacy and the fair use of genetic information; and public and professional education.

NCHGR is addressing these areas in two ways, through the research and education projects funded by the ELSI Branch and through the activities of the NIH/DOE Joint Working Group on Ethical, Legal, and Social Implications of Human Genome Research (ELSI Working Group).

Ethical issues surrounding genetics research: The ELSI Branch co-sponsored a workshop with the National Centers for Disease Control and Prevention (CDC) on "Informed Consent for Genetics Research Using Stored Tissue Samples." Based on the discussions at this meeting, a draft statement has been developed containing recommendations regarding informed consent using stored samples. These recommendations will be published and disseminated to Institutional Review Boards for their use in reviewing research proposals in which stored tissue samples will be utilized. The ELSI Branch will continue to examine and comment upon ethical issues related to genetics research and encourage further deliberations about these important issues among researchers and regulating bodies, such as the Office for Protection from Research Risks and Institutional Review Boards.

Responsible clinical integration of new genetic technologies: During FY 1994, NCHGR, along with the National Cancer Institute, the National Institute for Nursing Research and the National Institute of Mental Health, funded eleven, 3-year research projects to examine issues surrounding testing and counseling for heritable breast, ovarian, and colon cancer risks. The ELSI Branch will oversee all of these projects and is organizing a consortium of the Principal Investigators of these projects to pool resources, reduce duplication of effort, and assure coordination of the various studies. Through these studies, much evidence will be gathered about testing and counseling for genetic predispositions to cancer. The interest in and demand for testing, the impact of testing, and alternative ways to provide such services will be examined.

The number of genetic tests becoming available for use is increasing rapidly. Many tests to identify those with genetic diseases, those at increased risk of having children with genetic disorders, and those who have a genetic predisposition to develop disease are now available. The ELSI Working Group has created a Genetic Testing Task Force that will examine the many issues surrounding the utilization of genetic tests. The goals of the Task Force are to review the "state of the art" of genetic testing, examine the strengths and weaknesses of current practices and policies relating to testing, and if needed, recommend changes or policy options that will assure that the public is protected so that only the appropriate tests are done by qualified laboratories. The Task Force should complete its work by the end of FY 1996.

Privacy and fair use of genetic information: With the advent of new technologies to identify more genetic information about individuals, issues concerning the privacy and fair use of this information must be addressed. The ELSI Working Group has interacted with legislators and regulators on issues of the potential problems arising from the possibilities for stigmatization and discrimination. For example, the Working Group interacted with those drafting health care reform legislation about the possible risk of insurance discrimination based on genetic predisposition to disease. It also interacted with individuals interpreting the Americans with Disabilities Act to inform them of the risk for discrimination associated with such predisposition. This year the Working Group had an opportunity to comment upon model legislation related to privacy, which included language about genetic privacy, and is now reviewing a new model for privacy legislation. In the coming year, further efforts will be made to ensure that genetic information is neither misinterpreted nor misused.

Public and professional education: The ELSI Branch has funded a number of educational efforts designed to increase the level of knowledge of health and other professionals and the general public. Examples are projects designed to educate judges and journalists about developing genetic technologies; to develop a high school science curriculum; to update a current curriculum for high school biology students; and to educate consumers and health professionals about genetics and genetic technologies. ELSI is in the process of evaluating its education portfolio to identify gaps in public and professional knowledge. Subsequently, FY 1996 funds will be used to focus on high priority areas in genetics education.

Training and Outreach Programs

The extramural program of the NCHGR continues to increase the number of non-biologists and minority scientists who are involved in the Human Genome Project. NCHGR supports six scientists under the Special Emphasis Career Award Program. The NCHGR staff is currently working with universities and medical schools to develop the types of interdisciplinary training programs that train non-biologists and biologists in genomic sciences. NCHGR continues to strengthen efforts to support and encourage minority students and faculty to participate in the Human Genome Project. The NCHGR now supports 12 minority pre-doctoral students through National Research Service Awards and three students and four faculty members through minority supplements. Eight training courses have been funded in such areas as genetic linkage analysis, computational biology for molecular biologists, genomic technologies, and the ethical, legal and social issues that surround genomic research. The NCHGR will continue its efforts to train the type of scientists that will develop and utilize the technologies of genomic research, to get more individuals form under-represented groups involved in the Human Genome Project, and to disseminate genomic tools and technologies to the broader biomedical research community.

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act.
1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
80	$18,824,000	135	$39,389,000	135	$40,543,000	--	+$1,154,000

Since its establishment in February 1993, the NCHGR Division of Intramural Research (DIR) has made tremendous strides in establishing a flourishing research program and in forging collaborative ties with a number of other Institutes, Centers, and Divisions (ICD) at the NIH. The three Laboratories (Cancer Genetics, Genetic Disease Research, and Gene Transfer) and three Clinical Branches (Medical Genetics Branch, Diagnostic Development Branch, and Clinical Gene Therapy) are operational and nearly fully staffed. Core facilities are in place to support some of the research needs of scientists at NIH.

Funding for the intramural research activity follows:

Year	Amount	FTE
FY 1994	$18,824,000	80
FY 1995	$39,389,000	135

Rationale for the Budget Request

The FY 1996 request is $40,543,000, an increase of $1,154,000, or 2.9 percent, over the FY 1995 estimate of $39,389,000. This increase includes funds for intramural investigators who will be developing gene therapy treatments for different genetic diseases or those with a genetic component. A selected subset of the current and planned research activities in the Division of Intramural Research are identified below.

Gene Therapy

NCHGR is carrying out a comprehensive program involving the development of gene therapy applications for a diverse spectrum of diseases ranging from rare genetic diseases to common medical problems such as AIDS and cancer. The first authorized clinical trial of gene therapy continues with the ongoing study of two girls with a rare inherited immune deficiency disease called adenosine deaminase (ADA) deficiency. This treatment has resulted in restoration of normal ability to fight off infections and has permitted these children to resume an essentially normal life. This treatment appears to be safe and the gene-corrected cells are surviving in their bodies for many months longer than originally anticipated. During the past year, three newborn infants who had been diagnosed by prenatal testing as being afflicted with this disease were treated with ADA gene therapy immediately upon birth by inserting the gene into stem cells collected from their umbilical cords and placentas. The early results in these stem cell treated babies are very encouraging. We will continue intensive followup of these infants to determine whether this treatment strategy may provide them with a life-long cure of their disease. Similar treatments will soon be available for many other genetic diseases of the bone marrow, blood and immune systems.

Techniques of gene transfer seem to be advanced enough to permit their effective use in several different approaches to cancer treatment including attempts to produce a cancer vaccine by genetically modifying a cancer cell to make it more "visible" to the immune system. In another approach to cancer gene therapy, a gene called *"tk"* from the herpes virus is inserted into the tumors of patients with terminal brain cancer. This herpes virus tk gene encodes a protein enzyme that can in turn activate an anti-viral drug which will then kill the virus. In this form of gene therapy, the herpes tk gene becomes part of the metabolism of the brain tumor so that when the anti-viral drug is given, the tumor itself is killed. Results are encouraging enough that a multi-center trial of this treatment has been instituted at four different university medical centers across the country. In the coming year, a new kind of genetically engineered virus will be used which the preclinical studies in animals suggest may be as much as 10 times more potent than the virus used for gene transfer in the original clinical trial in brain cancer. In addition, the use of the tk system will be tried in several other forms of cancer such as ovarian and breast cancer.

Basic Research on Gene Transfer

The Laboratory of Gene Transfer is engaged in a number of projects aimed at uncovering the genetic basis of disease, and then using that information to develop new therapies. For example, last year a major gene for breast cancer (BRCA1) was uncovered by NIH and NIH-supported investigators. Research in the Laboratory of Gene Transfer has revealed that families with many cases of breast and ovarian cancer often have mutations in BRCA1, confirming that this is the correct gene. Moreover, the range of mutations found has been quite broad, indicating that the development of a DNA test for cancer predisposition will be technically challenging. The genetic basis of common diseases is one of the major frontiers for future advances in medicine. At the Laboratory of Gene Transfer two challenging projects have just gotten underway, aimed at identifying the genetic basis of adult-onset diabetes--(which affects 6.57 million Americans) and of prostate cancer--which affects 200,000 Americans. In both conditions there is strong circumstantial evidence of genetic predisposition, but the exact locations of the contributing genes have not been determined. With recent advances of the Human Genome Project, genetic maps and better technology, even these very difficult problems can now be approached.

Cancer Genetics

Scientists now understand that cancer arises when a normal cell acquires mutations in genes which control cell growth. Investigators in the Laboratory of Cancer Genetics are devoted to identifying those genes which are targets of alteration in tumorigenesis. This knowledge has immediate application for improved diagnosis of cancer and cancer risk and holds promise for improved strategies of cancer prevention and treatment. Advanced technologies for tumor chromosome analysis based on chromosome microdissection have been developed which have enabled the identification of chromosomal segments altered in malignant melanoma and cancers of the breast, ovary, and prostate. The gene hunting techniques of positional cloning are being utilized to map genes in the chromosome segments which have shown tumor specific abnormalities. This work produced DNA probes which are being evaluated in clinical studies correlating genetic alterations in tumors with the tumor's clinical properties in cancer patients. One such probe shows promise as a molecular marker of prognostic significance in prostate cancer, and additional probes are being developed for similar studies in melanoma, breast and ovarian cancer. Potentially useful probes are being made available to collaborating academic medical centers for evaluation.

Diagnostic Development Branch

The Diagnostic Development Branch conducts basic research and applied technology development related to the causes, diagnosis, and prevention of genetic diseases and cancer. Research currently focuses on the causes of human chromosomal abnormalities involved in pregnancy loss, early infant mortality, growth and developmental delay, birth defects with no known etiology, and various cancers. Basic research is also being conducted to identify the specific genes involved in the pathophysiology of diseases which result from an abnormal number of copies of a gene (other than two) or from the recently discovered phenomenon of genomic imprinting, in which the genetic consequences depend on the parent from whom a chromosomal abnormality is inherited.

In addition to these basic research priorities, the Diagnostic Development Branch is committed to the development and application of modern molecular genetics and genomics technologies for clinical diagnostics. Thus, it has established a strong team of investigators using cutting edge molecular technologies to improve diagnosis of genetic disease, including cancer. These translational research efforts include molecular diagnosis from single cells, digital imaging for high-resolution analysis of chromosomal abnormalities and gene amplification events in cancer, and the further development of the physical map of the human genome for application to diagnostics. In the coming year, these technologies will be validated through clinical research protocols, and then transferred to academic centers and to the commercial sector.

Genetic Disease Research

In the past year, the Laboratory of Genetic Disease Research has made a number of strides in accomplishing its mission. A major achievement was the identification of the p16 gene, which is involved in all cell control, as the major gene responsible for familial melanoma. This opens the door for development of more accurate diagnostic tests for at-risk individuals, and eventually for more effective treatments for this common and dangerous malignancy. Also in the area of gene identification, the location of genes responsible for the Wolfram syndrome and for proximal symphalangism was determined.

In the area of mouse models for disease, mice showing variable defects in kidney development and kidney function have been generated through manipulation of embryonic stem cells called "gene knockout" technology. Such mice represent useful model systems for studying normal kidney development and function. A gene knockout program was established, staffed, and equipped in FY 1994. In FY 1995 and beyond, this program will provide access to powerful technology for other researchers at NCHGR and other components of NIH studying a wide variety of genetic disorders.

Medical Genetics

Investigators within the Medical Genetics Branch examine and counsel individuals and families with genetic conditions, with the objectives of, identifying the genetic contributions to the cause of these disorders and, characterizing the clinical and natural history of conditions that have not been previously well-characterized. A general genetics protocol has been recently approved to study the clinical and molecular manifestations of six categories of genetic disorders, and patient recruitment and evaluation have been initiated and will continue vigorously in FY 1996. In addition to the study of rare genetic disorders, the Medical Genetics Branch will also be involved in evaluating genetic contributions to more common conditions, including malignancies of the breast, colon, prostate, and disorders affecting skeletal growth, including osteoporosis and osteoarthritis. The Family Studies Core, housed within the Medical Genetics Branch, provides an organized and effective resource for investigators throughout the NIH to study large families with inherited conditions.

Multidisciplinary research into the psychological sequelae experienced by individuals and families at risk for specific hereditary conditions, especially specific hereditary malignancies, has been initiated and will be a major focus of effort in FY 1996. This research will focus on the most effective and least harmful manner to communicate risk information to these individuals and families.

The Medical Genetics Branch has taken the lead role at NIH in medical genetics training. This program will continue to grow in FY 1996 with the advent of a new training program for genetic counselors. The clinical and laboratory research and training program for MD and PhD Fellows is a collaborative effort involving several institutes within the NIH, including the National Cancer Institute, the National Institute for Child Health and Human Development, the National Eye Institute, and academic institutions in the Washington, DC area.

National Center for Human Genome Research

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act.
1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
59	$6,181,000	61	$6,410,000	61	$6,601,000	--	+$191,000

This budget activity provides the staffing and resources for the overall leadership and fiscal management of the NCHGR, and administrative and scientific management of the Center's Division of Extramural Research. The Office of the Director sets policies and develops management strategies for both the extramural and intramural programs, and coordinates the NIH human genome program with those of other agencies and international organizations. The Division of Extramural Research plans and develops scientific initiatives in areas that best achieve the goals of the Human Genome Project (HGP). The Office of Scientific Review coordinates the review of research and research training applications. The Office of Administrative Management performs a variety of activities associated with the general business operations of the NCHGR, including financial management, human resource development, grants management, and general administrative services. A newly established position, that of Assistant Director for Policy Coordination, was created to oversee a variety of activities, including planning and evaluation, legislative affairs, public communications, and coordination of policies related to legal, ethical, and social implications of the HGP.

Funding for the research management and support activity during the last five years has been as follows:

Year	Amount	FTE
FY 1991	3,717,000	37
FY 1992	4,926,000	44
FY 1993	5,617,000	52
FY 1994	6,181,000	59
FY 1995	6,410,000	61

Rationale for the Budget Request

The FY 1996 request for the research management and support activity is $6,601,000, an increase of $191,000, or 3 percent, over the FY 1995 estimate of $6,410,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of Full-Time Equivalent Employment

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	6	7	7
Office of Admin. Management	23	23	23
Office of Human Genome Communications	2	3	3
Office of Program Planning and Legislation	7	7	7
Office of Scientific Review	7	7	7
Div. of Extramural Research	14	14	14
Div. of Intramural Research	80	135	135
Total	139	196	196

	Average GS/GM Grade
1991	9.8
1992	10.1
1993	10.2
1994	10.3
1995	10.4
1996	10.4

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Estimate
ES-6	3	3	3
ES-4	2	3	3
ES-3	1	1	1
Subtotal	6	7	7
GS/GM-15	11	12	12
GS/GM-14	10	14	14
GS/GM-13	10	12	12
GS-12	16	22	22
GS-11	20	22	22
GS-10	1	3	3
GS-09	14	16	16
GS-08	3	5	5
GS-07	19	19	19
GS-06	4	5	5
GS-05	3	4	4
GS-04	4	3	3
GS-03	1	1	1
GS-02	1	2	2
Subtotal	117	140	140
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Senior Grade	1	1	1
Full Grade	1	2	2
Senior Assistant Grade	1	2	2
Subtotal	3	5	5
Ungraded	37	53	53
Total positions	163	205	205
Total full-time equivalent employment, end-of-year	139	196	196
Average ES level	4.8	4.7	4.7
Average ES salary	$110,583	$112,242	$114,094
Average GS/GM grade	10.3	10.4	10.4
Average GS/GM salary	$ 42,972	$ 45,971	$ 47,105

THURSDAY, MARCH 23, 1995.

OFFICE OF THE DIRECTOR

WITNESSES

DR. RUTH L. KIRSCHSTEIN, DEPUTY DIRECTOR, NIH

DR. HAROLD E. VARMUS, DIRECTOR, NIH

DR. WILLIAM HARLAN, ASSOCIATE DIRECTOR FOR DISEASE PREVENTION

DR. LEAMON M. LEE, ASSOCIATE DIRECTOR FOR ADMINISTRATION

STEPHEN A. FICCA, DIRECTOR, OFFICE OF RESEARCH SERVICES

DR. VIVIAN W. PINN, ASSOCIATE DIRECTOR, OFFICE FOR RESEARCH ON WOMEN'S HEALTH

DR. JOHN RUFFIN, ASSOCIATE DIRECTOR, OFFICE FOR RESEARCH ON MINORITY HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. We're pleased to welcome again Dr. Ruth Kirschstein, the Deputy Director of NIH to the witness table to join Dr. Varmus. I understand that both of you will testify on the Office of the Director and Buildings and Facilities. You have assembled perhaps the largest team at the table we've seen yet. Why don't you introduce them.

INTRODUCTION OF WITNESSES

Dr. VARMUS. It could have been bigger. We're trying to restrain ourselves. At my far left is Dr. Leamon Lee, who's the Associate Director for Administration, and Dr. Vivian Pinn, whom you've met before, who's the Associate Director for Research on Women's Health, and Dr. William Harlan, Director of the Office of Disease Prevention, and Mr. Steve Ficca, Director of the Office of Research Services. Dr. Kirschstein, is the Deputy Director of NIH, and Dr. John Ruffin, is the Associate Director for Research on Minority Health.

OPENING STATEMENTS

As you know, Mr. Porter, the multiple affairs of the Office of Director have been conducted jointly by me and Dr. Kirschstein, and we will make a joint presentation.

I wanted to start with some general principles by which the Office of the Director is currently operating. We are operating in a difficult environment. In this environment of fiscal stringency and more oversight, the Office of the Director is taking on expanded responsibilities to ensure two things. First, that the Institutes, Centers and Divisions are working in a coordinated fashion to exploit scientific opportunity and to maximize efficiency, so we can come back to you every year with the same excitement and productivity we've come to you with this year.

Secondly, we want to ensure that our policies on many complex issues, issues that range from scientific priorities to technology transfer and training, are developed by consensus across the NIH and applied uniformly. My role today is to report briefly on a few things before I turn the microphone over to Dr. Kirschstein, who will report on the activities of several of the important offices that are embedded within the Office of the Director. She will also talk about our request for buildings and facilities.

First, let me remind you briefly how we're strengthening the intramural scientific program at NIH through the Office of the Director, mainly through the Deputy Director for Intramural Research, Dr. Michael Gottesman, who is ill and can't be with us today. His office has had a major role in implementing the recommendations of our external advisors report, a report that was mandated by this committee two years ago and has provided us with many important guidelines for our review procedures, and for the ways in which we recruit our scientists and promote them to tenured positions.

That implementation has proceeded rapidly. A report of the implementation process, which we could provide to you, made a major change in the way scientific life is conducted on campus, in our peer review, and given us a more competitive edge to the way in which we proceed on campus.

The intramural program has benefitted by the development of special interest groups that cut across the Institutes and develop camaraderie among scientists with similar disciplinary concerns. The central office has developed means for sharing resources within the intramural program, so that regardless of what Institute you're in, you can gain immediate computer access to expertise, instrumentation, or other materials that are available elsewhere on campus.

We've been carrying out reviews of our programs in a trans-Institute way, our animal facilities and our imaging methods in particular. The intramural program has also benefitted from new recruitment devices. We now have, thanks in part to the encouragement of your committee, the authority to use so-called Title 38 that allows us to recruit clinical investigators through enhanced salary opportunities. We will soon have available the Senior Biomedical Research Series that your committee has often urged us to obtain. And we have delegations of hiring authorities that are very important to us.

Similarly, the Office of Extramural Research, headed by Wendy Baldwin, has helped us in altering peer review processes, which as you know are essential to our ability to fund the best possible science. The peer review mechanism is part of a reinvention laboratory designated by the Department. Those overseeing the peer review process have put into effect a number of cost saving and efficiency mechanisms, including triaging of applications and simplifications of the application process. We are also working our way towards electronic submission of grant applications.

We've been very enthusiastic from the start about re-invention of Government and streamlining. Through a leadership retreat organized by my office we have pursued a number of initiatives that are intended to decrease the number of administrative positions at NIH and to improve our ratio of supervised to those who are supervising. We have initiated a study of a number of innovative methods to decrease costs for example, the generation of competitive service centers to carry out functions that are trans-Institute. We are also pursuing innovative methods in procurement and personnel and many other areas of administration.

We've set into motion methods to re-engineer our databases through the use of computers. We have other re-invention laboratories that I haven't mentioned. And we have used a resource allocation group, again trans-Institute in nature, to ensure that we remain below our FTE ceilings at all Institutes.

I mentioned to you earlier in response to a question our efforts to improve our ability to communicate findings of our Institutes to the public. We held a workshop, as you heard earlier, that was very successful and gave us a number of ideas about how to allow the public to gain more rapid access to information produced by our science.

We've also been reaching out to the local community in a variety of ways. As you know, we've had an uncertain relationship with some of the neighbors in Bethesda. Through a number of initiatives carried out by my office in the last year, we've appointed a community liaison. We have a community newsletter. We've had two public forums to interact with the community. Community members are now part of environmental working groups and planning groups for the future of our campus, and we are carrying out a soil testing program to evaluate concerns in the past about our incinerators, which have since been closed.

My office has been involved in a variety of policy and planning issues that extend across all the Institutes. We've been concerned with a number of issues involving in earlier testimony, technology transfer. Some of these came up in earlier testimony, including our policy on cooperative research and development agreements. We've had forums on so-called sponsored research agreements that occur at universities. We've settled a long-standing French and American dispute over HIV test kit royalties.

We've also discussed already this morning how we've evaluated the potential for doing work on in vitro fertilization. We are now in the process of putting together a round table on the economic benefits of biomedical research, an issue which I know is close to your heart. And as you heard from Dr. Collins, we are putting together and helping to support a panel that will be evaluating the implications of genetic testing.

We have also been coordinating scientific issues of broad interest. I've brought in external people to advise us on the use of the 1 percent transfer authority that this committee granted to us. That group of consultants has advised us to move ahead on re-programming to allow more rapid pursuit of opportunities in DNA sequencing in small angle x-ray defraction, and in mapping of the rat genome. We have in motion a review of our gene therapy procedures, including the process by which gene therapy protocols are being reviewed by the recombinant DNA advisory committee.

One other major scientific issue that has been pursued by the Office of the Director in a trans-Institute fashion concerns clinical research. I have named Dr. Lawrence Shulman, who was previously the Director of the National Institute of Arthritis, Musculoskeletal and Skin Diseases, to serve as my emissary to clinical research investigators in the extramural community. We are carrying out a survey of clinical trials monitoring. We've been concerned about training in clinical investigation. We've established a new training program for clinical investigators at the clinical center. We have been evaluating the way in which clinical research grant applications have been reviewed by the Division of Research Grants, and that's resulted in some changes in how we review such applications. And I'm currently forming a standing panel of clinical investigators to provide me with general advice about how clinical research is pursued in this country.

I should give you a brief report on the use of the Director's discretionary fund. Last year, most of the funds were used for Shannon awards. These are small awards given for two years, $50,000 per year, to allow young investigators in particular, who didn't succeed in obtaining an RO–1 award, to nevertheless get started in research. We fund those in collaboration with the Institutes in a 40 percent, 60 percent ratio.

In addition, we used some of the discretionary fund to support exciting research, particularly in neurobiology, that fell just below the pay line. We also used some of our discretionary monies to initiate a loan repayment program, which was mentioned briefly to Mr. Stokes a few days ago, in which clinical investigators from disadvantaged backgrounds can come to NIH for a couple of years to obtain training in clinical investigation while paying back their education loan.

EEO issues have been of traditional interest to this committee. Before I turn the microphone over to Dr. Kirschstein I should just mention briefly that since we've been delegated authorities for making our senior executive service appointments, roughly half of our 26 SES-level hires have been women, and a third have been minorities. In addition, we've been able to settle a pay equity plan for our intramural women and minority scientists.

So having gone over a large number of general trans-Institute policy issues, I'd like now to ask Dr. Kirschstein to review some of the specific activities of the offices within the Offics of Director and to review the buildings and facilities program.

Dr. KIRSCHSTEIN. Thank you, Dr. Varmus.

Mr. Porter, you commented on the large group of people that we have at the table. We have a number of others who support us in the Office of the Director who are sitting behind us. We chose to put forward at the table people who do a great deal of the work and whom you very often do not see. And we thought that it would be appropriate for you to see them, and to give them an opportunity to answer any questions that you may have about their specific areas.

We have a number of offices that have been set up for specific purposes, which this committee particularly and the Congress in general has been interested. One of these is the Office of Research on Women's Health, which Dr. Vivian Pinn heads, and which has been involved in a number of activities, which facilitate action on the issues related to women's health as put forward by our Institutes.

And I should say that all of the offices in the Office of the Director work primarily by facilitating the mission of NIH through the Institutes. We also have the Office of Research on Minority Health, Dr. John Ruffin is the Associate Director. One of the exciting things that Dr. Ruffin has been involved in this year has taken advantage of the discovery of the "obesity" gene by grantees of the National Institute of Diabetes, Digestive and Kidney Diseases. And as you know, obesity is a problem of all Americans, but, there are some differences in some ethnic groups. Hispanic women and men, to some extent, as well as other minorities are particularly affected. Dr. Ruffin has been providing funds and working with Dr. Gorden, Director for NIDDK, and his staff to provide to funds to the Rockefeller University to continue this work.

Dr. Varmus mentioned the SES appointments. I want to also emphasize that we are committed to diversity in our work force. We have begun to expand these commitments in a number of ways. We are actively engaged in a two track process. First we are continually examining and evaluating our various affirmative actions and special emphases programs. In addition, we have developed a new affirmative action planning process. We think that this will balance the competing interests of diversity, as well as those required by downsizing. Dr. Varmus has mentioned the need to streamline, and we have been working very hard on the streamlining processes that are required. But we want to be sure, as we go about this process, that our plans do not, in any way, provide any implications that will prevent us from continuing to have a diverse work force.

Dr. William Harlan, who is the Associate Director for Disease Prevention, is also responsible for the Women's Health Initiative. You may remember that this committee asked us to have the Institute of Medicine do a study on the Women's Health Initiative, and that report was presented last year. The Women's Health Initiative is going extremely well. It is on target and has enrolled a large number of individuals. Some of its activities are beginning to be modified, because as we told Ms. Lowey on the first day of these hearings, and Dr. Harlan can elaborate, a study performed primarily in the National Heart, Lung and Blood Institute, the so-called PEPI study, has made it clear that the hormonal therapies that were planned must be modified. Dr. Harlan can elaborate on that.

Now, the appropriation funds for the Office of the Director also include funds for one of the newest offices, the Office of Alternative Medicine. The budget request will allow the Office of Alternative Medicine to expand its research endeavors. It has been functioning under an Acting Director, Dr. Alan Trachtenberg, who is with us today. We are very pleased to tell you, what you probably have seen already in the newspapers, that we will be having a new director, Dr. Wayne Jonas, who comes to us from the Walter Reed Army Institute for Research. He has been working with us, although he will not be coming on board for some time.

One of the things that the Office of Alternative Medicine has been doing is reaching out to communities that have not been a part of the traditional NIH group of grantees. We have awarded a center grant for the first time to a Naturopathic College of Medicine to try to collect data on what we know is happening, yet we do not know in great detail, the various therapies that are being used by individuals who have HIV infection and AIDS. These therapies that are not within the sphere of traditional medical practice, yet we know they are being used widely. Therefore, we will have such a compendium of such therapies which I think will be useful to Dr. William Paul and the Office of AIDS Research when it is completed.

The fiscal year 1996 request for the Office of the Director itself is $230,256,000.

Now, I'd like to turn to the Buildings and Facilities appropriation, which is handled by Mr. Stephen Ficca, of our Office of Research Services. It provides funds for the design, construction, improvement and major repairs of our clinical laboratory and office buildings. As you know, the NIH is contending with an aging and very deficient physical plant. The majority of the infrastructure systems at NIH are anywhere between 20 and 40 years old, and they are beyond the life span anticipated by their design.

The need for a new facility for the most important and exciting clinical research that we do in the NIH Clinical Center was affirmed by the external advisors that Dr. Varmus mentioned. And so we are planning a unique new facility to be able to conduct "state of the art" clinical research. We have discussed this with you previously, and within the Buildings and Facilities request $23,000,000 is requested for the first stage of planning and upgrading this hospital, which will be smaller than our current hospital facility. Again, on the advice of the external advisors, it will be about 250 beds, and will also contain the laboratory space needed for research in support of clinical studies.

I think we should make it clear that, in our buildings and facilities program, what we are doing is placing our greatest priority on the essential safety and health requirements of our facilities. We want these to be able to meet the necessary occupational and environmental requirements to protect and support the ongoing research programs, and to protect the safety and health of our employees. The fiscal year request for the Buildings and Facilities is $144,120,000.

My colleagues and I would be pleased to answer any questions and to expand as you wish.

[The prepared statement and biography of Dr. Ruth Kirschstein follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Deputy Director of the National Institutes of Health Office of the Director and Buildings and Facilities

I am pleased to have the opportunity to be here today to discuss with the Committee the FY 1996 budget requests for the Office of the Director (OD) and for the Buildings and Facilities account.

Office of the Director

The Office of the Director provides leadership and direction to the NIH research community, and coordinates and directs initiatives which cut across the NIH. The OD, under Dr. Varmus, is responsible for the development and management of intramural and extramural research and research training policy, the review of program quality and effectiveness, planning and evaluation, technology transfer, coordination of selected NIH-wide program activities such as research on women's health, minority health and disease prevention, as well as the administration of centralized support activities essential to the operation of the NIH.

The OD has established the Office of Behavioral and Social Sciences Research to develop, coordinate, and implement an overall NIH research strategy for the conduct and support of behavioral and social science research. The office will also focus on educating the biomedical community and the general public about the role of individual, familial, social and environmental factors in the promotion of good health and the prevention, treatment, and cure of disease. This office has an appropriation of $2,240,000 in FY 1995 which will increase by about $200,000 in FY 1996.

The budget request provides funds for the Office of Research on Women's Health (ORWH) to continue to refine and expand its programs and activities, to address the inclusion of women in clinical research, and to promote biomedical careers for women. In addition, the ORWH will develop new collaborative initiatives to address continuing gaps in knowledge about women's health which affect both mortality and morbidity. The research agenda will identify newly evolving areas of women's health not previously defined or recognized. I am also pleased to inform you that the Women's Health Initiative is progressing extremely well and is well within budget. Enrollment from diverse populations is assured by special emphasis on Hispanic women in the Southwest and on Black women.

The budget request continues funding of the Minority Health Initiative (MHI) which builds on the previous NIH efforts to improve the overall health of minorities and to provide training to more minority biomedical researchers. Further, we will continue initiatives, in collaboration with several institutes, to address newly emerging areas of research such as: effects of migration on health; health and behavioral effects of lead exposure in childhood in inner city neighborhoods; and the health of minority women. In addition, we plan to expand all our minority research training efforts.

The NIH is committed to diversity within its workforce, a diversity which recognizes both the rights and the responsibilities of all employees. We are actively engaged in a two-track process in support of this commitment. One is a continuing and critical examination and evaluation of various affirmative action and special emphasis programs, as part of our overall streamlining effort. We intend to ensure more efficient utilization of NIH staff and fiscal resources while continuing to assure recruitment and promotion of women and minorities. The second track is the development of a new affirmative action planning process that balances the competing interests of diversity and of downsizing. We are confident that these efforts will promote our objectives even further.

The OD also recently established the Loan Repayment and Scholarship Programs. The Clinical Research Loan Repayment Program allows qualified health professionals from disadvantaged backgrounds to conduct clinical research within the NIH intramural programs for a minimum period of two years. In return, the NIH agrees to repay their educational loan debt up to a maximum of $20,000 annually. The Undergraduate Scholarship Program provides scholarships to individuals from disadvantaged backgrounds. Awards are made to undergraduate students who agree to pursue academic programs towards careers related to the health professions of importance to NIH. Students agree to work at NIH for one year for each year of scholarship aid after graduation. The OD budget request also includes funds for the General Research Loan Repayment Program which is intended to recruit and retain, in non-trainee positions, physicians and scientists engaged in both basic and clinical research activities at the NIH.

Funds for the Academic Research Enhancement Award (AREA) program are also included in the OD budget request. This program provides grants through the various Institutes and Centers, to enable faculty members, in educational institutions that are not research-intensive, to participate in the nation's biomedical and behavioral research effort. These AREA grants provide support, in particular, for small undergraduate colleges, thus, giving incentives and educational opportunities to students to enter research careers.

Finally, this appropriation funds the Office of Alternative Medicine (OAM). The budget request will allow the OAM, under the leadership of its new Director, to expand its research endeavors and to collaborate with the Institutes, Centers and Divisions (ICDs) to increase studies directly supported by them. Within the ICDs approximately $13 million is being expended on research on alternative therapies, related to their specific missions. The funds requested by the OAM will expand and improve such research endeavors. We are delighted that the new Director, Dr. Wayne Jonas will be joining us full time in June, although, he is spending considerable time with us already.

The fiscal year 1996 request for the Office of the Director is $230,256,000 and includes additional funds of $4,500,000 for the Office of Research on Women's Health; $4,500,000 for the Minority Health Initiative; $1,396,000 for the Academic Research Enhancement Award Program; $2,032,000 for the Loan Repayment and Scholarship Programs and $3,363,000 in support of the Office of Research on Minority Health, the Office of Alternative Medicine, the Office of Rare Diseases, as well as Science Education.

The Buildings and Facilities appropriation provides funds for the design, construction, improvement, and major repair of clinical, laboratory, and office buildings, as well as supporting facilities, essential to the mission of the NIH. The impact of the Buildings and Facilities program has never been more critical in terms of shaping and defining the very essence of the NIH campus as we approach the twenty-first century. At the same time, we must meet the essential near-term needs of the central plant facilities and utility distribution systems necessary to support ongoing research activities at the NIH.

The NIH is contending with an aging, deficient physical plant. The majority of the infrastructure systems are 20 to 40 years old and beyond the life span anticipated by their design. To address these deficiencies and to plan for the future, the NIH is integrating all corrective actions and new construction programs into a comprehensive Facilities Revitalization Program. This program represents a long-term strategy to coordinate projects and set priorities so that ongoing laboratory and clinical research, as well as anticipated technological advancements can be supported with modern facilities.

The NIH has placed a high priority on the renewal of the Clinical Center Complex (CCC), a unique facility for the conduct of state-of-the-art clinical research. It contains approximately 40 percent of the research space on the Bethesda campus and is the keystone of the NIH Intramural Research Program. The evolution of the CCC over the past 40 years has resulted in utility infrastructure systems that are old, outmoded, obsolete, and insufficient to support modern research. The NIH has developed plans to renew the complex consistent with the recommendations contained in the External Advisory Report on the NIH Intramural Research Program.

The renewal program will ultimately provide an upgraded Clinical Center Complex with a new hospital of about 250 beds and laboratory space to support the clinical research program. This will be followed by a sequential, phased renovation of the original structure to house the major portion of remaining laboratories and other functions currently in the Clinical Center. This FY 1996 request will provide for the design, development and related construction activities for the hospital and laboratory addition.

Based on an independent study by the U. S. Army Corps of Engineers, the Round Robin Program was reevaluated in 1993. It was determined to be unadvisable from an engineering and research standpoint to renovate Buildings 2, 3, and 7 as laboratory buildings. The construction of the Consolidated Laboratory Building was recommended to replace completion of the Round Robin Program and provides the necessary laboratory space lost by these buildings.

NIH continues to place a high priority on the Essential Safety and Health requirements of its facilities. Infrastructure upgrades to existing NIH facilities are necessary to meet critical occupational and environmental requirements to protect and support ongoing research programs, including the safety and health of NIH employees and patients. Supporting utilities need to be modernized and improved in order to meet safety and health requirements in support of the NIH research mission.

Other funds included in the FY 1996 request for the Essential Safety and Health initiative are for the improvement of outdoor air quality by upgrading the power plant's infrastructure, for the phased removal of asbestos containing materials from NIH buildings, for the upgrade of the fire and life safety equipment, and for the revitalization of facility reliability and safety upgrades at the Rocky Mountain Laboratory in Hamilton, Montana. Also included in this request are funds for the elimination of barriers to persons with disabilities, the initial implementation for the study, design, and construction of a multi-year program to address indoor air quality concerns in NIH facilities, and the construction of a new fire station on campus needed for emergency responses.

Funds are requested that will complete the ongoing construction of the laboratory addition at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. This laboratory addition will replace costly leased laboratory facilities. Funds are also requested for the final annual payment to the Department of the Treasury for claim settlement in connection with Turner Construction Company.

The FY 1996 request for Buildings and Facilities is $144,120,000. The request includes $57,570,000 for essential safety and health improvements, $23,000,000 for the design development and related construction activities for the new hospital and laboratory addition, $32,723,000 for the completion of construction for the Consolidated Laboratory Building, $19,427,000 for the continuing program of repairs and improvements, $6,000,000 for the continued funding for the replacement facilities at the NIEHS, and $5,400,000 for the final payment related to the Turner Construction claim.

My colleagues and I would be pleased to respond to your questions, Mr. Chairman.

BIOGRAPHICAL SKETCH

Ruth L. Kirschstein, M.D.
Deputy Director
National Institutes of Health

Dr. Ruth L. Kirschstein's distinguished career as both a scientist and administrator in the U.S. Public Health Service (PHS) has spanned a period of 36 years. A trained pathologist, she made a series of highly significant contributions to biomedical research between 1957 and 1972 as a result of her laboratory work in the Division of Biologics Standards (then part of the National Institutes of Health; later transferred to the Food and Drug Administration and first renamed the Bureau of Biologics and, most recently, the Center for Biologics Evaluation and Research). She has over 70 scientific publications to her credit.

Among her most notable scientific achievements is the development, refinement, and application of a test that provided a means for assuring the safety of viral vaccines such as those for polio, measles, and rubella. It was largely as a result of the studies carried out by Dr. Kirschstein and her staff that the "Sabin strains" were accepted as being the most suitable for the oral polio vaccine. The impact of the vaccine's subsequent use was dramatic: it virtually eliminated a disease that only a few years earlier had struck 37,000 people annually.

Because of the success of her work in this area, Dr. Kirschstein became a recognized authority on the performance and interpretation of safety test results and on the neurovirulence of viruses. On several occasions, she served as a consultant to the World Health Organization on such matters. In addition, her expertise was utilized by many biological manufacturers who requested her help in perfecting their testing procedures.

Dr. Kirschstein has also made significant contributions as a research administrator, first as Assistant Director (1971-1972) and Acting Deputy Director (1972-1973) of the Bureau of Biologics, then as Deputy Associate Commissioner for Science of the Food and Drug Administration (1973-1974). From 1974 to 1993, she was the Director of the National Institute of General Medical Sciences (NIGMS), one of the National Institutes of Health (NIH). In addition to directing NIGMS, from September 1990 to September 1991, Dr. Kirschstein also served as the Acting Associate Director of the newly established NIH Office of Research on Women's Health. Since July 1993, she has been the Deputy Director of NIH; from July to November 1993, she was also the Acting Director of NIH.

The first woman to serve as an institute director at NIH, Dr. Kirschstein has provided strong scientific leadership for NIGMS' research programs, which make over 3,000 grant awards each year. She has facilitated coordination and collaboration with other NIH components, federal agencies, and private organizations, and has engendered solid support in both the public and private sectors for the basic biomedical research and research training activities of the Institute.

Under Dr. Kirschstein's direction, NIGMS gained international recognition for the excellence of its programs in such areas as genetics, structural biology, cellular and molecular biology, pharmacology, and biorelated chemistry. She promoted the establishment of a critically important resource for genetics research, a nucleotide sequence data bank known as GenBank that has a pivotal role in efforts to sequence the human genome. She also strengthened the Institute's commitment to another major research resource, the Human Genetic Mutant Cell Repository. Cells from this repository are playing an increasingly important role in research on genetic diseases.

In addition to her support of NIGMS' general research training activities, Dr. Kirschstein oversaw the expansion of two specialized training efforts. The Minority Access to Research Careers Program, which was formally established in 1975, aims to increase the number of minority scientists engaged in biomedical research and to strengthen science curricula and research opportunities at institutions with substantial minority enrollments. The Medical Scientist Training Program, which was created in 1964 but grew rapidly during Dr. Kirschstein's tenure, seeks to reduce the nationwide shortage of physician-researchers by enabling highly qualified students to obtain a combined M.D.-Ph.D. degree.

In 1989, NIGMS took over administration of the Minority Biomedical Research Support Program, which funds research grants and enrichment activities at minority institutions. With the transfer of this program, NIGMS became the major focal point at NIH for minority biomedical research and research training activities.

Shortly after becoming NIGMS Director, Dr. Kirschstein was asked to chair a study team that was charged with thoroughly examining the NIH grants peer review system, identifying its strengths and weaknesses, and making recommendations as to how it could be improved. Peer review is central to the operation of the NIH grants and contracts program, and it is critical that the system operate both fairly and effectively. Dr. Kirschstein's efforts resulted in a report that was both timely and comprehensive, and many of its recommendations were implemented. Two major changes that resulted from the report were the release of the summary statements prepared following the initial review groups' deliberations and the creation of formal opportunities for applicant investigators to comment on and appeal the review groups' recommendations. In 1987 and 1988, Dr. Kirschstein also participated in an NIH committee that identified and assessed more recent issues related to peer review.

Other committees and task forces on which Dr. Kirschstein has been an active participant include the Congressionally mandated Task Force on Women, Minorities, and the Handicapped in Science and Technology (1987-1990), the NIH Task Force on Predoctoral and Postdoctoral Training of Non-Physician Scientists (1989), the NIH Advisory Committee for the Institute of Medicine Study of the Organizational Structure of the NIH (1983-1984), the NIH Coordinating Committee on Manpower (1978-1983), and the Fogarty International Center Scholars-in-Residence Advisory Committee (1977-1982).

Dr. Kirschstein currently co-chairs the PHS Coordinating Committee on Women's Health Issues, which grew out of a PHS Task Force on Women's Health Issues that she headed in 1983 and 1984. In addition, she is a leader in NIH activities related to biotechnology and minority biomedical research and training, and served as chairperson of the NIH Working Group on Minorities in Biomedical Research. Dr. Kirschstein co-chairs the Department of Health and Human Services (DHHS) Secretary's Special Emphasis Oversight Committee on Science and Technology. She is also a member of the Advisory Council for the "First Light" Program at the Carnegie Institution of Washington; the National Critical Technologies Panel; the Advisory Committee for Biological Sciences of the National Science Foundation; and the DHHS Executive Development Board.

Dr. Kirschstein was elected to the Institute of Medicine of the National Academy of Sciences in 1982. In 1985, she received the Presidential Rank Award for Distinguished Executives, the highest honor that can be given to a career civil servant. She was selected by the Office of Personnel Management in 1989 as one of 10 outstanding executives and organizations for its first group of "Profiles in Excellence." The American Medical Association honored Dr. Kirschstein in 1990 with its Nathan Davis Award to a member of the Executive Branch in career public service. She is also the recipient of the 1993 Public Service Award from the Federation of American Societies for Experimental Biology.

Among her other honors are the Executive Excellence Award for Distinguished Executive Service from the Senior Executives Association (1985); the Presidential Meritorious Executive Rank Award (1980); Superior Service Awards from PHS (1978) and the Department of Health, Education, and Welfare (1971); a PHS Special Recognition Award (1985); and the PHS Equal Opportunity Achievement Award (1983). Dr. Kirschstein was given the Harvey Wiley Food and Drug Administration Commissioner's Special Citation in 1987. She received honorary Doctor of Science degrees from the Mount Sinai School of Medicine in 1984 and the Medical College of Ohio in 1986. In 1985, Atlanta University awarded her an honorary Doctor of Laws degree. In 1991, Dr. Kirschstein received an honorary Doctor of Humane Letters from Long Island University. She was elected as a fellow of the American Academy of Arts and Sciences in 1992.

Dr. Kirschstein was born in Brooklyn, New York, on October 12, 1926. She received a B.A. from Long Island University in 1947 and an M.D. from Tulane University School of Medicine in 1951. After an internship in medicine and surgery, she took residency and fellowship training in pathology.

February 1994

UNOBLIGATED CONSTRUCTION BALANCES

Mr. PORTER. Dr. Kirschstein, of the $114,000,000, I believe that there's $64,000,000 from the current fiscal year that remains unexpended, is that correct?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. PORTER. Assuming that the rescissions are adopted?

Dr. KIRSCHSTEIN. Yes, that's right.

Mr. PORTER. Not much more?

Dr. KIRSCHSTEIN. Yes. In the rescission that has passed the House, $50,000,000 was rescinded from the Buildings and Facilities program, that's correct. So Mr. Ficca can speak to that in detail.

Mr. PORTER. Well, is the $64,000,000 included in your $114,000,000, I guess is my question?

Mr. FICCA. The number is $144,120,000 in the FY 1996 request. In FY 1995 the appropriation is $114,120,000.

Mr. PORTER. A hundred forty-four.

Dr. KIRSCHSTEIN. Yes, and the 64.

Mr. FICCA. I think the $64,000,000 are the funds that were originally appropriated for the two other projects which were never obligated, that is, the consolidated office building and the laboratory building. Those were appropriated through fiscal year 1995, and yes, some of that would have been included, but it would have been appropriated prior to 1996.

[The following information was provided subsequent to the hearing:]

The $64,000,000 is the amount that would remain after the proposed rescission of $50,000,000 is deducted from the approximate $114,000,000 in unobligated balances that are uncommitted and available for the Building and Facilities.

Mr. PORTER. There's $114,000,000 in carryover funds, is that correct?

Mr. FICCA. Yes sir, Mr. Porter, the $114,120,000 FY 1995 appropriation would have been in addition to the previously appropriated unobligated amounts that are B&F carryover funds.

Mr. PORTER. If we did not rescind them, right.

Dr. KIRSCHSTEIN. Yes. The $114,120,000 in FY 1995 is in addition to the carryover funds.

PUBLIC OUTREACH

Mr. PORTER. All right, that's what I'm trying to get at.

Well, first of all, Dr. Varmus, I'm sorry that in your description of all the efficiencies and innovations that are going on in the Office of the Director that my new Members weren't here to hear this, because I think that's exactly what they need to hear. And it's the kind of thing that any Member of the Appropriations Committee wants to hear, and I want to commend you for what you're doing. I think you're doing exactly what we want you to do, looking at ways to save money and do things better and more cheaply and still get the same quality result. And that's to be commended.

You talked about public outreach. And if I can just lobby you for a minute and say that I would love to see something on National Public Television, a series on biomedical research that would be like the Carl Sagan series on space exploration and understanding the universe. I think it would be exciting television, I think it would capture the imagination of the people who saw it, and it would keep them up to date on all the exciting things going on at NIH and in the world of research that I otherwise don't think there really is an outlet that really reaches people.

Dr. VARMUS. Public television has been carrying such shows. There was an eight part series last year that was very effective. My previous colleague, Michael Bishop, whom you met at the Nobel laureates hearing, will be the host of a two or three part series that will be run in a few months. In addition, as I mentioned previously, we're currently negotiating with the Maryland Public Broadcasting System for what we hope to be a weekly show on health and health research that we believe would be an important showcase for NIH-sponsored activities.

Mr. PORTER. And so you are working with the local station to provide the programming. Are you doing anything with PBS directly?

Dr. KIRSCHSTEIN. The Public Health Service, through Dr. Lee, the Assistant Secretary for Health, has an individual who is working with the Public Broadcasting System out of New York, and has been talking with Anne Thomas, the Director of the NIH Office of Communications. She and he are going to work together on some activities.

PROFUSION OF SPECIFIC OFFICES

Mr. PORTER. One further question. As you described the various offices, Dr. Kirschstein, in almost every case, these are offices that were requested by Congress. And maybe with all the people sitting at the table, this is not a fair question. But what if Congress said, you don't have to have all these offices, you can arrange these kinds of concerns any way you want to arrange them. And we'll provide adequate funding, but you don't need to have all these different offices. Would that be appealing or not?

Dr. KIRSCHSTEIN. Of course, Mr. Porter, that was the way NIH was a number of years ago. These offices are new creations within the Office of the Director.

Mr. PORTER. They are political creations in a certain sense. These are important concerns, don't get me wrong. But they are in response to politics, and I think politics has a place, but it shouldn't have too much of a place in science. I think science should arrange itself whatever way it thinks it should be arranged.

Dr. KIRSCHSTEIN. Having said that, I think that there is value, and I think Dr. Varmus indicated this in some of the things he has stated this morning, in having the Office of the Director with its oversight, with its ability to assess the broad picture, have units which can facilitate the work that the Institutes do. These individual offices have interactions with specific communities, with women who are interested in women's health, with the minority community, and with the community that is interested in alternative medicine; and the broad community across all medical sciences interested in disease prevention. These offices have the means to facilitate studies and fill in the gaps in which there may not be quite as much work as there should be. In general, these offices also provide to Dr. Varmus the advice that is needed to really do such studies in the appropriate manner.

MINORITY HEALTH INITIATIVE

Mr. PORTER. The Minority Health Initiative, unlike the Women's Health Initiative, which is one project with a very clear goal, is a combination of many small programs to support diverse areas, such as disease research, training, infant mortality, and violence. What is the long-term plan for the Minority Health Initiative? Do you see a continuation of the current approach, or does minority health merit the same kind of focused initiative as women's health?

Dr. KIRSCHSTEIN. The Women's Health Initiative, of course, was set up because of particular interest in a special series of diseases suffered by the women of this country, and by individuals who felt that these diseases were important. I think the health areas in which there are difficulties for minority populations, and the diversity of minority populations, for example, blacks, Hispanics, Pacific Islanders, American Indians, probably need a more diverse approach.

In addition, I think work is already in progress in the various Institutes, work on hypertension and sickle cell disease in the Heart Institute, on particular cancers, for example, cancer of the uterine cervix in minority women in the National Cancer Institute. As some of the Institutes were already working in those areas, the Office of Research on Minority Health can provide additional funds. And I think Dr. Ruffin might want to elaborate a bit.

Dr. RUFFIN. Thank you. I listened very carefully this morning, Mr. Porter, to the presentation by Francis Collins, which clearly showed that there are individuals in our country whose health is at great risk. I also listened to the discussion that Dr. Collins had with Mr. Obey, related to the ethical issues involving those same individuals. I think that when we look at it on a somewhat larger scale, we can say that the health of minorities in this country is also at great risk.

We certainly look at our office within the Office of the Director as an extension of the Institutes, not as two separate entities. We look at ways of trying to help the Institutes to expand what they do, and to do that job a lot better and faster. If you look at how we spend our dollars in the office, in terms of the Minority Health Initiative, I think what you would see is three scenarios.

On one hand, looking at some of the programs that are supported by the Institute, we use many of the dollars in our office to expand some of the ongoing initiatives. For example, work may have been done extensively on one ethnic group to the exclusion of another, we then try to use some of the dollars to expand research into those areas.

Another scenario is, we try to fill what the community calls gaps. In other words, we are interested in what is it that we should be doing on the health of minority individuals that we're not doing. We try to serve as a kind of a listening post to a great extent for the various Institutes—to listen to what the community is saying and to bring this information back to the Institutes—and not just to bring it back, but to bring it back and to work with the Institutes to convert that information that we hear to good science. And in these instances, we use our dollars in partnership with the Institutes as a leveraging mechanism.

A third scenario is the use of money from our office to support pilot initiatives. Now, in the long run, at the end of the road here, what is it that we expect? At some point, our hope is that upon evaluation, we find that these initiatives are working, and that the health of minority people is improving. The hope is that the Institute will then pick up these pilot projects, and that they will become a part of the Institute's funded portfolio. There would be no need for an office like our office when in fact the health gap of minority people begins to decrease and decrease significantly, so that we can see that there is an improvement in the health of minority people.

Dr. KIRSCHSTEIN. Let me add a couple of things to that. Actually, Dr. Pinn's office does somewhat the same activities through her other programs. The Women's Health Initiative, which was a term, as you know, coined by Dr. Healey was developed as a separate entity from Dr. Pinn's office. Dr. Pinn's office does exactly the same thing that Dr. Ruffin does, but this is not what is called the Women's Health Initiative.

In addition, I think we should state that both of those offices are now going to be seeking even more broadly than they have in the past, outside advice from a number of experts in the areas, so that we will be refining their programs.

FUTURE CAMPUS CONSTRUCTION

Mr. PORTER. This is a question for either Dr. Kirschstein or Dr. Varmus. You seem to have two major construction priorities, the clinical center and the consolidated lab building. Do you expect any further campus construction to be necessary beyond these few projects?

Dr. VARMUS. Not in the foreseeable future. Not before the year 2000.

CLINICAL CENTER REPLACEMENT

Mr. PORTER. Okay, then, Dr. Varmus, I'd like to give you the opportunity to lay out for the record what failure to replace the clinical center facility would mean for your intramural clinical research program. Would there be other ways to conduct this sort of research off campus?

Dr. VARMUS. It would be extremely difficult. As you know, Mr. Porter, one of the things that characterizes the intramural program is the centrality of our clinical research effort. Nowhere else in the country do we have the number of clinical research beds that are adjacent to research laboratories.

In fact, clinical research of the kind we do at the clinical center is being quite severely threatened by changes in health care practice throughout the country, with decreased revenues from patient sources to support the clinical research activities of academic health centers. So the NIH clinical center, which has been the source of almost half of the clinical research beds in the country, becomes even more important.

It is not clear how much longer we can operate that hospital, because of the severe physical deterioration of the building. The only way we can operate clinical research units on campus is by building a hospital of the sort we've recommended. If we were to have to move our facilities to other sites, while I wouldn't say it would be impossible, the efficiency and strength of the research program would be very severely curtailed. It would take the heart out of the intramural program and make it a much less attractive site for training and clinical investigation and for basic investigation that relates to clinical goals.

Mr. PORTER. Mrs. Lowey, I want to apologize to you. I was so intent on listening to what the testimony was, I didn't realize you were here. Mrs. Lowey.

PLANNED WOMEN'S HEALTH INITIATIVES

Mrs. LOWEY. Thank you, Mr. Chairman. I appreciate it. And thank you, Doctors, and I appreciate your being here before us today.

I want to just state at the outset that I personally appreciate the important work of the Office of Research on Women's Health. In fact, when I came to Congress in 1988, whether it was a political decision or otherwise, it's always so hard to say, but it seemed to many of us, particularly in the Congressional Caucus on Women's Issues, that women's health, despite the best intentions of the scientific establishment, had been neglected far too long.

And I personally, on behalf of the Caucus and so many of us, appreciate the important advances in women's health that have come about as a result of the Office. We are very, very appreciative. And I want to thank you all for your leadership.

In the testimony, it stated that there will be new collaborative initiatives to address continuing gaps in knowledge about women's health. Perhaps Dr. Pinn or Dr. Kirschstein, could you discuss the initiatives you may have planned, where can we hope to go this year in women's health research. Are there areas of greater need?

Dr. PINN. There are certainly many areas of need. But, let me first say thank you for your support and interest in what we're doing which we've very much appreciated over the years.

There are so many areas that we feel still need to be addressed in women's health, not just areas related to the reproductive system, but many other areas that we try to prioritize each year, areas on which we should focus, areas on which we don't see active research or a significant amount of research to redress some of those gaps in knowledge.

Right now, among many issues, including behavioral issues, substance abuse issues, violence issues, looking at not just diseases, but health and prevention and preservation of health as well as basic science mechanisms of diseases and their ramifications, we're focusing on four to five major areas that we feel need to be targeted.

One has to do with autoimmune disease in women. There's a lot of concern, for example, about lupus and about the role of immune diseases in relationship to female hormones and the implications of pregnancy in such diseases. There are many things we don't understand. We really don't understand even why we see these immune diseases affecting women more than they affect men. This is an area that we're working on with both NIAID as well as NIAMS. We've had some special initiatives that we started last year and now we're working to put into place some others to address major questions in this and other research areas.

Another example is that of women's urinary health. We all know urinary tract infections are very common in women. But, we really don't understand the mechanisms, and there has not been a lot of basic research on just the normal physiology of the female bladder. Urinary incontinence, which many people think of as just affecting older women, is a condition that affects younger women, too, and it deserves research into both clinical as well as basic science mechanisms. Interstitial cystitis, which is not as common, but certainly is a severe problem for women that are affected by this disease, also needs more research.

Many reproductive issues are high priority; some of those are related to conditions that serve as indicators for hysterectomy. While we do not research hysterectomy as such, we are looking at endometriosis and fibroids as well as other conditions that lead to hysterectomy. We have an ongoing project with the Nursing Institute and I believe it's Aging, to look at decision making relating to hysterectomy.

We are also focusing on menopause, both in terms of its being a consequence of a surgical or chemical intervention as well as natural menopause in women. These studies are in addition to the Women's Health Initiative.

[CLERK'S NOTE.—Subsequent to the hearing, it was indicated that the ORWH is collaborating with AHCPR, not Aging, on the project on decision making related to hysterectomy.]

We're also beginning to look at areas related to future women's health issues, such as the legal and ethical implications of genetic testing as it affects women especially, and many other areas that I could go on with. But these are some of our major areas that we're focusing on.

INDIRECT COSTS

Mrs. LOWEY. Certainly the area, if I'm correct, of menopause was neglected for as far back as my knowledge takes me. And in talking to women of my generation, it's amazing how little knowledge they have when they have to make very important decisions. I'm particularly pleased to know about the work that's being done on estrogen replacement therapy. Women just aren't given all the information they need. And if they are given all the information, it's inadequate to make an appropriate decision at the appropriate time. So I'm particularly pleased, and I hope that all the work that's being done will lead to some informed decisions. And we thank you very much.

We could go on, but because of the limited time, there's another area that I've been deeply interested in, and that's the whole area of indirect costs. In the budget justification, it states that "NIH is currently participating in the research subcommittee of the National Science and Technology Council's Committee on Fundamental Science. This subcommittee was charged with the task of reviewing costs of research with special emphasis on reimbursement for research facilities."

You also mentioned the President's cost principles for educational institutions. We also know that the issues of indirect costs is a very complicated one, and I fear that for too many people, they're led to believe that indirect cost is synonymous with waste, fraud and abuse. And I think that deserves clarification.

Certainly, we have to curb any abuses in Federal support for research, but that research cost legitimately includes a portion of any institution's overhead costs. Could you, Dr. Varmus or whoever would like to respond, elaborate for the subcommittee on where NIH is on the issue of indirect costs. It's a complicated issue, and I hope you will take the opportunity to explain how institutions determine their indirect cost rates, and what types of expenses those costs include.

Dr. VARMUS. Thank you for the question. We've discussed this earlier, I think, in response to a question from Mr. Porter. But let me review some of the things that were said then and perhaps say a few additional things. The NIH is working very closely with the Department of HHS, indeed with a number of other agencies across Government through the Office of Science and Technology Policy, to try to clarify some of the issues you just raised.

I agree with you that through a number of unfortunate events, overhead (or indirect) costs have been confused in the public mind with a number of unfortunate episodes. One of the things that's being done to try to change that perception is to recognize that these costs are part of the real costs of doing research. We now think of the Government's support of research as total costs. These are composed of the project expenses (that is, salaries and supplies for the actual doing of the research); the administrative costs (which are incumbent in any institution that receives grant support); and the facilities costs (required to supply the rooms in which the research is done, the utilities, and other special costs, such as animal care facilities).

We are attempting to try to understand more clearly how different rates obtain in different institutions. As you know, administrative costs have been capped at 26 percent for a few years now. Now all institutions are able to live within that 26 percent cap. So the differences in rates that you've referred to can be assigned to the facilities rates. Those facilities rates are determined by negotiation between Federal representatives and the institutions that receive NIH support. And as you also probably know, the facilities rates can vary from as low as 15 percent or so up to the range of 50 percent of the project costs.

We are engaged in a study to try to understand those differences before we carry out any changes that might impair the institutions that carry out research. We would like to try to normalize rates. We would like to try to make the determination of those rates simpler and more easily explained to the public. We would like to try to establish the differences in costs for construction and maintenance of facilities in a way that allows us to establish benchmarks for such costs, so that the negotiation process can proceed through an understanding of what normal costs are in a region for certain kinds of institutions.

As you know, state facilities frequently have an advantage of lower rates because the states do supply some of the facilities costs. And in general, we know that a major determinant of differences in facilities rates can be ascribed to the nature of the institution.

Other differences include the area of the country, because utilities demands and costs vary in different parts of the country. We're trying to do a survey—in which a number of agencies in the Government are participating, but NIH is taking a very principal role—to understand the nature of those differences and to normalize the accounting process and the rate negotiation as much as possible. We expect to have that completed within the next year.

Mrs. LOWEY. Thank you very much, and I know the majority of Members on this committee will continue to support investments in research, because we certainly think that the cost benefit analysis proves the case that these investments are cost effective.

Unfortunately, I have to go, but I look forward, Dr. Pinn, Dr. Kirschstein, Dr. Varmus and Doctors, to being briefed in the near future on the Women's Health Initiative, where it is and your plans for this year, whether it's necessary for the record or whether we can have a more informal conversation, we'd be most appreciative.

And I thank you, Mr. Chairman.

Dr. KIRSCHSTEIN. We will make plans for such a briefing.

Mrs. LOWEY. Good. Thank you very much.

INDIRECT COSTS FOR FACILITIES

Mr. PORTER. If I can follow up briefly on that, Dr. Varmus, I understand that some indirect costs of facilities rates are much higher than 50 percent. You said 15 to 50 percent was the range?

Dr. VARMUS. That's approximately right. I think there are probably a few outliers that are higher than that. Remember that that's facilities rate alone. There's of course an additional 26 percent for administrative costs.

Mr. PORTER. Maybe that's what we were talking about.

Dr. VARMUS. I think so, yes. Because the——

Mr. PORTER. For example, Johns Hopkins, I think, was at 66 percent.

Dr. VARMUS. Yes, but 26 percent of that would——

Mr. PORTER. Yes. And I also understand that institutions borrowed money and built facilities to do research on the assurance that they would be able to recover those costs if they were successful in getting grants for projects. And the suggestion that we could somehow cap this would mean, well, you tell me what it would mean. What if we were to cap it at a total of 50 percent, including the administrative costs? What would it mean to institutions who compete for grants?

Dr. VARMUS. Well, for some institutions this could be a penalty. We're reluctant to try to impose a cap without further understanding why the rates vary. Now, a component of the study that we're carrying out is directed to the question that you raised, that is, how do institutions recover the interest on the loans that they may have obtained to build their buildings.

We want to understand that, we want to look at the use to which buildings are put per square foot, and we would like to understand the metrics a little more closely than we do before we try to make any recommendations such as a cap, which could be penalizing to institutions, many of which are our best institutions, that do have some of the highest rates.

Mr. PORTER. How many institutions are we talking about, if I asked you to provide to me all of the institutions and their various rates? Would that be very——

Dr. VARMUS. Well, every institution has a rate. We could very easily provide to you the 100 institutions that have the largest amount of NIH funding.

Mr. PORTER. Why don't you do that?

Dr. VARMUS. Certainly, we could supply that.

Mr. PORTER. Both for the record and for us to see.

Dr. VARMUS. Yes.

[The information follows:]

Top 100 Colleges and Universities Receiving NIH Research Grant Funding in FY94

Sorted (high to low) by NIH Funding Dollars

			FY95 Rate
1		JOHNS HOPKINS UNIVERSITY	66.50%
2		UNIVERSITY OF CALIFORNIA SAN FRANCISCO	44.50%
3		UNIVERSITY OF WASHINGTON	48.50%
4		UNIVERSITY OF MICHIGAN AT ANN ARBOR	52.00%
5		YALE UNIVERSITY	64.00%
6		UNIVERSITY OF PENNSYLVANIA	63.50%
7		UNIVERSITY OF CALIFORNIA LOS ANGELES	49.00%
8		WASHINGTON UNIVERSITY	54.00%
9		COLUMBIA UNIVERSITY NEW YORK	70.00%
10		STANFORD UNIVERSITY	58.03%
11		UNIVERSITY OF CALIFORNIA SAN DIEGO	50.50%
12		DUKE UNIVERSITY	52.00%
13		UNIVERSITY OF PITTSBURGH AT PITTSBURGH	50.50%
14		UNIVERSITY OF NORTH CAROLINA CHAPEL HILL	44.50%
15		UNIVERSITY OF WISCONSIN AT MADISON	43.00%
16	*	HARVARD UNIVERSITY - MEDICAL SCHOOL	79.90%
16	*	HARVARD UNIVERSITY - SCHOOL OF PUBLIC HEALTH	48.80%
17		UNIVERSITY OF MINNESOTA TWIN CITIES	45.00%
18		CASE WESTERN RESERVE UNIVERSITY	51.00%
19		UNIVERSITY OF ALABAMA AT BIRMINGHAM	43.00%
20		BAYLOR COLLEGE OF MEDICINE	48.00%
21		UNIVERSITY OF SOUTHERN CALIFORNIA	63.50%
22	**	NEW YORK UNIVERSITY	55.50%
22	**	NEW YORK UNIVERSITY - MEDICAL CENTER	67.50%
23		UNIVERSITY OF COLORADO HLTH SCIENCES CTR	51.50%
24		UNIVERSITY OF TEXAS SW MED CTR/DALLAS	54.00%
25		VANDERBILT UNIVERSITY	56.00%
26		YESHIVA UNIVERSITY	65.90%
27		UNIVERSITY OF CHICAGO	55.00%
28		UNIVERSITY OF IOWA	46.00%
29		EMORY UNIVERSITY	57.00%
30		UNIVERSITY OF ROCHESTER	57.00%
31		MASSACHUSETTS INSTITUTE OF TECHNOLOGY	52.00%
32		UNIVERSITY OF CALIFORNIA BERKELEY	49.50%
33		UNIVERSITY OF MIAMI - MEDICAL SCHOOL	53.50%
34		CORNELL UNIVERSITY MEDICAL CENTER	69.82%
35		BOSTON UNIVERSITY	65.00%
36		UNIVERSITY OF VIRGINIA CHARLOTTESVILLE	53.00%
37		UNIVERSITY OF ARIZONA	51.50%
38		MOUNT SINAI SCHOOL OF MEDICINE	64.50%
39		UNIVERSITY OF UTAH	49.50%
40		UNIVERSITY OF CALIFORNIA DAVIS	44.00%
41		UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANTONIO	45.00%
42		WAKE FOREST UNIVERSITY(BOWMAN GRAY SCH OF MEDICINE)	45.00%
43		UNIVERSITY OF MARYLAND BALTIMORE PROF SCHOOL	45.00%
44		OHIO STATE UNIVERSITY	46.00%
45		THOMAS JEFFERSON UNIVERSITY	67.00%
46		UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER	48.00%
47		INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	50.00%
48		UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON	49.00%

		FY95 Rate
49	UNIVERSITY OF FLORIDA	44.00%
50	OREGON HEALTH SCIENCES UNIVERSITY	46.00%
51	UNIVERSITY OF CALIFORNIA IRVINE	49.50%
52	ROCKEFELLER UNIVERSITY	54.70%
53	NORTHWESTERN UNIVERSITY - CHICAGO	47.50%
54	UNIVERSITY OF CINCINNATI	53.00%
55	STATE UNIVERSITY NEW YORK STONY BROOK	48.10%
56	WAYNE STATE UNIVERSITY	51.00%
57	VIRGINIA COMMONWEALTH UNIVERSITY	45.00%
58	GEORGETOWN UNIVERSITY	61.00%
59	UNIVERSITY OF ILLINOIS AT CHICAGO	48.35%
60	UNIVERSITY OF MASSACHUSETTS MEDICAL SCH	57.00%
61	DARTMOUTH COLLEGE	63.00%
62	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON	50.50%
63	CORNELL UNIVERSITY ITHACA	65.08%
64	MEDICAL COLLEGE OF WISCONSIN	50.00%
65	TUFTS UNIVERSITY BOSTON	64.00%
66	UNIVERSITY OF CONNECTICUT HEALTH CENTER	48.00%
67	UNIVERSITY OF KENTUCKY	49.00%
68	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE	50.90%
69	HARVARD UNIVERSITY - CAMBRIDGE	69.50%
70	UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN	54.20%
71	TULANE UNIVERSITY OF LOUISIANA	51.00%
72	TEMPLE UNIVERSITY	53.00%
73	STATE UNIVERSITY OF NEW YORK AT BUFFALO	52.00%
74	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	41.80%
75	MICHIGAN STATE UNIVERSITY	47.00%
76	MEDICAL UNIVERSITY OF SOUTH CAROLINA	44.00%
77	PURDUE UNIVERSITY WEST LAFAYETTE	51.00%
78	RUTGERS THE STATE UNIV NEW BRUNSWICK	59.00%
79	CALIFORNIA INSTITUTE OF TECHNOLOGY	60.00%
80	PENNSYLVANIA STATE UNIV HERSHEY MED CTR	48.50%
81	UNIVERSITY OF COLORADO AT BOULDER	43.50%
82	UNIVERSITY OF TENNESSEE AT MEMPHIS	42.50%
83	COLORADO STATE UNIVERSITY	45.00%
84	UNIVERSITY OF TEXAS AUSTIN	50.50%
85	UNIV OF MED/DENT NJ-R W JOHNSON MED SCH	60.00%
86	UNIVERSITY OF NEW MEXICO ALBUQUERQUE	48.00%
87	UNIVERSITY OF MEDICINE & DENTISTRY OF NJ	60.00%
88	HEALTH SCIENCE CENTER AT BROOKLYN	49.30%
89	TEXAS A&M UNIVERSITY HEALTH SCIENCE CTR	45.00%
90	NORTHWESTERN UNIVERSITY - EVANSTON	47.50%
91	UNIVERSITY OF KANSAS MEDICAL CENTER	49.00%
92	PRINCETON UNIVERSITY	59.00%
93	MEDICAL COLLEGE OF PA AND HAHNEMANN UNIV	57.00%
94	BROWN UNIVERSITY	58.00%
95	LOUISIANA STATE UNIV MED CTR NEW ORLEANS	42.00%
96	UNIVERSITY OF HAWAII AT MANOA	44.00%
97	ST. LOUIS UNIVERSITY	46.00%
98	GEORGE WASHINGTON UNIVERSITY	50.50%
99	INDIANA UNIVERSITY BLOOMINGTON	50.00%
100	UNIVERSITY OF ARKANSAS MED SCIS LTL ROCK	47.00%

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* Tracked by NIH within same accounting fund.

** Tracked by NIH within same accounting fund.

Dr. VARMUS. I should point out that there has been some decline in so-called indirect cost rates over the last few years in part due to the capping of the administrative costs, but also because of attention being paid to facilities costs as well. We expect that that can be further reduced in time by paying closer attention to how those rates are negotiated.

Dr. KIRSCHSTEIN. Mr. Porter, we are working on this entire subject with all of the other agencies that support scientific research through the National Science and Technology Council Committee on Fundamental Sciences and a subcommittee on research. NIH has probably the greatest, among the various agencies, expertise on this. But other groups from the Department of Defense, Department of Agriculture, National Science Foundation, have been deeply involved in this as well.

Mr. PORTER. It's my understanding that many institutions feel that a cap on indirect costs would be more devastating to their financial picture than even a reduction in the funds available for grants.

Dr. VARMUS. Well, I think it depends on the extent to which——

Mr. PORTER. I suppose it's on the particular institution.

Dr. VARMUS. And it depends on the amount of money we're talking about.

Mr. PORTER. Yes, of course.

Dr. VARMUS. But it is a serious concern, and I am particularly concerned about abrupt changes. I think institutions will be able to adjust to recommendations about how we manage facilities costs that are implemented over a prolonged period of time so that they can adjust their procedures. But abrupt changes are very devastating.

Mr. PORTER. Well, we thank you, Dr. Varmus and Dr. Kirschstein, and all of the people at the table and staff for your additional testimony today.

And the subcommittee will stand in recess until 2:30 p.m.

[Recess.]

[The following questions were submitted to be answered for the record:]

MASTER PLAN/FACILITIES REVITALIZATION

Mr. Porter: We understand that you are in the process of completing both a campus Master Plan and a facilities revitalization program. When will these two efforts be completed?

Dr. Kirschstein: The NIH Master Plan for the Bethesda campus will address the development of the site over the next 20 years and provide the overall direction to and coordination among individual physical infrastructure programs. A Draft Master Plan will be completed by June 30, 1995. Following public and agency review of this draft, as well as the associated Draft Environmental Impact Statement, a Final Master Plan is anticipated to be approved no later than December 31, 1995.

The NIH Facilities Revitalization Program is an ongoing integrated program of corrective and new construction projects with various components, as follows:

- Clinical Center Complex Renewal Program. New Hospital addition, modular development of new laboratory space and phased renovation of existing structure (see below).

- Essential Safety and Health Improvements. Special programs and initiatives necessary to provide a safe environment, ensure compliance with life-safety requirements and environmental regulations. Two of the major projects included in this program are:

    - Clinical Center Essential Maintenance and Safety Program. Phased restoration of utility systems and correction of life safety problems. This program is under way, with actual construction scheduled to begin in September 1995. The first two phases are scheduled for completion by September 1997, while the total Program is anticipated to be completed by the middle of 1998.

    - Infrastructure Modernization Program. Master Utilities Plan for the utility central plants and distribution systems has been completed. Several utility upgrade and expansion programs associated with these plans are planned and/or under way. Completion is anticipated by the end of 1999.

- Repair and Improvement Program. This program provides for major repairs and improvements to the physical plants of NIH facilities. The costs are either recurring or one-time expenditures for major items of equipment requiring emergency action. A lump-sum budget request is designated for these purposes and individually projects are prioritized so that the most critical projects are addressed, and some funds are available for inevitable emergencies.

- Renovation and Upgrading of Existing Buildings and Infrastructure
    - Rehabilitation of Laboratory Buildings (Round Robin). This is an ongoing program initiated in 1979. Buildings 8, 4, and 5 have been rehabilitated. NIH is proposing the construction of a Consolidated Laboratory Facility to satisfy the research space needs of Buildings 2, 3, and 7 (see below), conversion of Buildings 2 and 3 to administrative space, and subsequent demolition of Buildings 7 and 9. This program is anticipated to be completed by the end of the year 2000.
    - Intramural Animal Facilities Program. This is an ongoing upgrade and renovation program of NIH animal facilities to maintain accreditation by the American Association for the Accreditation of Laboratory Animal Care, which is essential to NIH's intramural research program. Completion is scheduled for 1998.

Mr. Porter: How can you go forward with your building plans before these master documents are developed?

Dr. Kirschstein: Currently, NIH is operating under the 1972 Master Plan. Though ideally an updated Master Plan should have been prepared prior to any revitalization efforts, the urgency of implementing corrective action to address life safety issues and infrastructure deficiencies required NIH to proceed with planning and implementation components of the revitalization prior to the completion of the Master Plan update. If a proposed construction project is not in conformance with the 1972 Master Plan, NIH can prepare and submit a Master Plan Amendment to the National Capital Planning Commission which covers the specific project until the total campus Master Plan has been completed.

Mr. Porter: The campus Master Plan has been under development for some time. Can you give us some idea of its major themes?

Dr. Kirschstein: A first draft NIH Master Plan for the Bethesda campus was prepared and submitted for agency and public review in the fall of 1993. In March 1994, following fundamental policy changes at the NIH and in the Federal Government, this draft was withdrawn from the public review process. The NIH began a comprehensive review of the basic assumptions of the Master Plan to incorporate Administration and NIH policies related to streamlining efforts, including the recommendations of the External Advisor's Report on the NIH Intramural Research Program and to provide for enhanced involvement of the neighboring communities.

These factors have prompted significant changes in the direction of the Bethesda campus Master Plan. Fundamental premises of the campus Master Plan include the following:

- Total population growth at the Bethesda campus over the next 20 years is anticipated to be no more than 10 percent of the 1993 population of 16,350. The primary growth at the campus is expected to be in intramural research personnel either from relocation and consolidation from other NIH facilities or from some future background growth in research programs.

- Based on the need to keep NIH research facilities current with codes, standards and technologies, replacement space may be required. Wherever possible, existing buildings will be altered for adaptive reuse.

- The existing Clinical Center Complex building will be maintained as part of a phased renewal program (see below).

- The second phase of the William H. Natcher Building will not be constructed (also see below).

CLINICAL CENTER RENEWAL

Mr. Porter: Have you finalized your design concept for the new Clinical Center complex, and can you describe it for us?

Dr. Kirschstein: The basic design approach for the renewal of the Clinical Center Complex has been established. A decision has been reached on the design concept for the initial phase of the renewal. This consists of a new downsized, inpatient hospital replacement located adjacent to and connected with the existing facility at the north side. Included will be a component of research laboratories for those programs that require contiguity with the hospital beds.

The second and any subsequent phase of the Clinical Center renewal would involve reconstruction of the older portion of the existing facility to support modern research. The scope, costs and schedules of this effort cannot be determined until the effects of the Intramural Research Program downsizing have been assessed and the ensuing facility needs established.

This design approach is consistent with the recommendations of the External Advisory Committee's Report of April 1994.

Mr. Porter: Is this approach consistent with the overall downsizing plan for intramural research? What share of campus intramural research will ultimately be located at the Clinical Center?

Dr. Kirschstein: This approach is fully consistent with the overall plan to streamline and downsize the Intramural Research Program. The inpatient bed complement will be approximately 250, a 40 percent reduction from the available beds at the end of 1994. This will result in improved hospital operating efficiencies and increased resource sharing among the users, thus reducing operating costs for patient care.

The proportion of intramural clinical and laboratory research ultimately located in the Clinical Center Complex will likely remain at about 40 percent.

Mr. Porter: How many square feet of usable space will the new Clinical Center have compared to the current facility?

Dr. Kirschstein: The existing Clinical Center Complex has approximately 3 million gross square feet of which approximately 1.25 million is net (usable) square feet. Phase I of the renewal effort will provide approximately 850 thousand gross square feet of new construction. The overall net square feet of the renewed complex cannot be determined until the effects of the Intramural Research Program downsizing have been assessed and the facility needs established.

Mr. Porter: What are your working assumptions about usage of the new Clinical Center in terms of inpatient days, inpatient occupancy rates, and outpatient visits?

Dr. Kirschstein: The working assumptions are:

- Inpatient days will remain about the same or decline slightly.
- Inpatient occupancy rates will go up substantially and the total number of beds will decrease.
- Outpatient visits will increase slightly.

Mr. Porter: Under your plan, what share of clinical research lab space will be contiguous to the hospital beds, and how does that compare with clinical research done at other facilities?

Dr. Kirschstein: Approximately 15 percent of the total research labs within the Clinical Center Complex will be located in the new construction. This is consistent with the views of the External Advisory Committee. A major design objective for the renewal of the Clinical Center is to provide the best possible adjacency for the remaining laboratories.

The issue of comparison with other clinical research facilities was also discussed with the External Advisors. It was concluded that there are no other facilities that have clinical research programs of the size, diversity and interaction that would make comparison meaningful.

Mr. Porter: How many years will it take to complete the work on the Clinical Center? Describe which components will be completed in which years.

Dr. Kirschstein: The new hospital/laboratory facility will require five to six years to complete under our current planning scenario. The scope and timing of the subsequent components cannot be determined at this time. However, there is a finite period of 12 to 15 years, confirmed through various engineering studies, in which to accomplish the Clinical Center renewal because of the deteriorating infrastructure.

Mr. Porter: Is the cost figure of $380 million your current estimate for the project? Does that represent total project costs or only the first phase of rebuilding the hospital (as opposed to renovating the existing structure)? Identify your projected funding needs for the Clinical Center construction by year.

Dr. Kirschstein: The $380 million is for the initial stage of the Clinical Center renewal, which is the design and construction of the new hospital and associated laboratory component. Following the FY 1996 funding request of $23 million for design development, the remaining funds of $357 million will be required for completion of the construction documents and construction. We are in the process of engaging the services of a development firm to generate various financing options that could reduce the impact of this project on our future budget requests.

Mr. Porter: When the Army Corps of Engineers endorsed the need for a new Clinical Center building several years ago, cost estimates of up to $1.6 billion were suggested. Please explain the main differences in the building configuration contemplated by the Corps and the design that is now anticipated, and explain why the cost estimates have been revised so substantially.

Dr. Kirschstein: The configuration endorsed by the Corps was a total replacement facility of about 3.5 million gross square feet located on a central site within the Bethesda campus. The $1.6 billion estimate included replacing older buildings that would be demolished to create an adequate site for the proposed complete Clinical Center replacement. The design now anticipated is for a limited new facility consisting of 600,000 gross square feet of hospital and hospital support and 250,000 gross square feet of directly related laboratory space.

Mr. Porter: How do you plan to finance this construction, and what financing alternatives did you consider?

Dr. Kirschstein: NIH is developing alternative financing approaches including funding mechanism(s) and sources. This should be completed by January 1996.

Mr. Porter: Last year, both the House and Senate reports urged you to consider reallocating existing resources, including intramural resources, to partially finance the costs of the facility. Is this part of your plan?

Dr. Kirschstein: Yes, existing resources will be reallocated to partially finance the cost of this facility. The amount of reallocated funds cannot be determined until NIH fully assesses the impact of the Intramural Research reforms.

Mr. Porter: Break out the expected use of the funds in your $23 million 1996 request for the Clinical Center Complex Renewal Program.

Dr. Kirschstein: The 1996 request of $23 million will fund detailed programming, schematics and design development for this project including developer services fees for design management. These deliverables form the basis for obtaining firm cost estimates for the construction phase, including project schedules and detailed construction documents.

Mr. Porter: If Congress weren't able to provide the funds for a new Clinical Center hospital, would renovation of the existing facility be an option you would consider?

Dr. Kirschstein: If construction of the new Clinical Center hospital is not possible, the condition of the existing facility is such that we have no option but a programmed major renovation to avoid catastrophic system failures. Such a renovation, without a new Clinical Center hospital, could not take place without relocating large portions of the research program to off-campus facilities. Market surveys conducted in support of the External Advisory's review indicated that there is not adequate Institutional or lease space available to accommodate this need.

Mr. Porter: What is the current projected lifespan of the Clinical Center Complex, assuming continued investment in the Essential Maintenance and Safety Program? If possible, break out useful life by component, such as the Ambulatory Care Center.

Dr. Kirschstein: The Essential Maintenance and Safety Program (EMS), with relatively minor impact to ongoing research, will correct failed or failing centralized systems in the old portion of the Clinical Center to enhance reliability and to extend their service life. (Only marginal capacity increases can be provided due to the limitations of the distribution systems.) The EMS is designed as an interim measure to extend the service life of the facility until a major renovation of the clinical center can be accomplished in 12 to 15 years.

The estimated service life for the Clinical Center with continued EMS funding still will not exceed 15 years. The piping, duct work and electrical distribution systems that are present throughout the occupied program areas have a life expectancy of 12 to 15 years. They cannot be replaced without vacating large amounts of space, which would result in a crippling impact on research programs if the new hospital addition is not completed. Neither the EMS nor the replacement of distribution systems will provide the capacities, flexibility or adaptability to modern research requirements.

The Ambulatory Care Research Facility addition, completed in 1980, should remain viable for the next 15 to 20 years.

Mr. Porter: Have any other facilities been considered as possible sites for the Clinical Center, such as the Bethesda Naval Center? What is your opinion of any such alternative sites?

Dr. Kirschstein: For the External Advisor's review of the NIH intramural research program, NIH surveyed all major hospitals in the Washington D.C. metropolitan area and conducted a detailed study and analysis completed March 1994 of four Government and three private facilities for hospital bed occupancy, laboratory potential and land availability.

The beds available ranged from fewer than 40 to 85. Only the USUHS had significant laboratory space, with 165,000 gross square feet potentially available for NIH use in the future. This space would require extensive renovation to meet NIH needs. None of the facilities could accommodate the research staff and support to go with the beds. None of them had land suitable for expansion to meet NIH needs.

The NIH has concluded that adaptation of other facilities for its clinical research program requirements was not feasible. This was discussed with and endorsed by the External Advisors.

Mr. Porter: How much will you have spent on Clinical Center essential maintenance and safety work by the time the new hospital is complete?

Dr. Kirschstein: The Essential Maintenance and Safety (EMS) Program is a finite program estimated to cost $73 million over four years including our FY 1996 request of $21 million. The EMS program, which started in FY 1994, will be completed before the new hospital completion.

Mr. Porter: Have any academic health centers or government agencies (such as the Department of Veterans Affairs) built research hospitals in the recent past which you can use as a rough guide to the expected costs of building a new Clinical Center? How do your estimated per square foot costs compare to those projects?

Dr. Kirschstein: The unit costs used to develop the project cost estimate of $380 million were generated from actual unit costs derived from over 24 completed laboratory and hospital projects of similar scope and three market surveys to arrive at the local geographical cost factor. These studies are available upon request.

Mr. Porter: Identify the 1994 - 1996 budget for the Clinical Center by major components and the source of its funding by institute.

Dr. Kirschstein: The original operating budgets of the Clinical Center for the three years were $221,743,000, $227,034,000 and $236,197,000 respectively. Surplus funds of $1.9 million and $7.5 million were returned to the individual institutes in FY 1994 and FY 1995. The FY 1996 budget level has been voluntarily reduced by $11 million due to decreased program requirements.

The major components of the budget are Patient Care Hospital Costs and Non-Hospital Costs. The allocated percentages are shown below.

Clinical Center Budget by Major Components
(Dollars in thousands)

Fiscal Year	Hospital Patient Care	Non-Hospital	Total
1994	$205,280	$14,542	$219,822
1995	$202,136	$17,364	$219,500
1996	$206,372	$18,859	$225,231

FY 1994 - FY 1996
Clinical Center Assessments
(Dollars in thousands)

	1994 Clinical Center Assessment	1995 Clinical Center Assessment	1996 Clinical Center Assessment
NCI	$89,790	$87,858	$93,101
NHLBI	28,777	28,177	27,509
NIDR	1,252	1,259	1,683
NIDDK	13,213	12,928	12,432
NINDS	16,991	16,884	17,989
NIAID	15,955	15,610	18,060
NIGMS	--	--	--
NICHD	13,408	13,117	11,111
NEI	4,383	4,290	4,529
NIEHS	--	--	--
NIA	3,241	3,360	3,991
NIAMS	4,361	4,270	4,557
NIDCD	381	487	721
NIMH	22,373	22,704	21,592
NIDA	--	--	--

	1994 Clinical Center Assessment	1995 Clinical Center Assessment	1996 Clinical Center Assessment
NIAAA	4,571	4,505	4,092
NINR	0	0	0
NCHGR	0	2,920	2,733
FIC	0	0	0
NLM	0	0	0
FDA	0	0	0
Subtotal	$218,696	$218,369	$224,100
Reimbursements	1,126	1,131	1,131
Total	$219,822	$219,500	$225,231

Mr. Porter: Identify the current inpatient occupancy rate for the Clinical Center as well as the rate for each of the last ten years. Has the share of research beds allocated to various Institutes changed significantly in the past ten years?

Dr. Kirschstein: The number of available research beds in the Clinical Center has declined over the past ten years. This reduction has been driven by the shift of medical treatment from an inpatient to an outpatient setting and the introduction of the Day Hospital concept for infusions and intermediate treatments. Although the number of available research beds in the Clinical Center has been reduced in the past ten years, this reduction has been distributed evenly across institutes. Clinical Center management is currently planning to reduce the number of available bed days to the 116,000 range by consolidating patient care units. This action was initiated at the recommendation of the group of external advisors who recommended a 250 bed facility. This consolidation has been planned with institute input so that the program needs of each will be met, while at the same time the Clinical Center can be operated in the most financially efficient manner possible.

Inpatient Occupancy Rate

Fiscal Year	Inpatient Days	Bed Days Available	Occupancy Rate
1986	108,906	174,950	62.2%
1987	105,882	178,120	59.4%
1988	113,042	179,460	63.0%
1989	104,730	177,400	59.0%
1990	98,276	171,550	57.3%
1991	90,037	165,710	54.3%
1992	87,521	153,665	57.0%
1993	78,048	147,460	52.9%
1994	72,167	139,065	51.9%
1995	72,240	145,635	49.6%

Mr. Porter: If Congress were not able to meet your full 1996 request for both the Clinical Center and the Consolidated Lab Building, would you proceed with both in a more limited way or delay the start of one?

Dr. Kirschstein: The importance of the Clinical Center project to the overall Intramural Research Program dictates that this project will proceed in full even if this means delaying the start of the Consolidated Laboratory Building.

CONSOLIDATED LABORATORY BUILDING

Mr. Porter: Implicit in your fiscal year 1996 request is an assumption about construction of the second phase of the consolidated office building. Could you formally tell us NIH's current position on this construction project, and why you think it is no longer needed?

Dr. Kirschstein: It is in the best interest of the government and the NIH mission to redirect the Natcher Building, Phase II (Consolidated Office Building) funds to the Clinical Center Complex Renewal (CCCR) program and the Consolidated Laboratory Building (CLB). NIH must address the safety of its employees as the top priority. The existing Clinical Center can no longer safely and adequately support the changing needs of NIH's patient care and research programs. The CLB is necessary to address the safety and functional deficiencies in Buildings 2, 3 and 7, which are to be replaced by the CLB. The extramural programs that were to have been relocated to the Natcher Building Phase II will remain safely housed in nearby leased facilities. This redirection of funds will eliminate potential environmental problems caused by deteriorating infrastructure. In contrast to the Natcher Building Phase II, the CCCR and the CLB represent no growth and directly address these critical safety issues.

Mr. Porter: Please describe your plans for a new Consolidated Lab Building: its total cost by year, the buildings it would replace, the comparison of square footage in the old buildings versus the new, its location on campus, its construction schedule, the planned use or demolition of the buildings it would replace, and the Institutes which would be anticipated to use the space. What share of the intramural lab space on campus would be located in the consolidated lab building.

Dr. Kirschstein: The Round Robin Program was approved by Congress in 1979 to provide major upgrading of the older research facilities on campus. This upgrade was deemed necessary since the infrastructures of these buildings could no longer safely support modern biological research. However a study by NIH and a review committee of the United States Army Corps of Engineers determined that renovating these facilities would not offer the flexibility and the reliability necessary for a modern biomedical research program due to the existing physical constraints that the renovations cannot modify. As a result, a plan was developed to relocate the laboratories housed in Buildings 2, 3 and 7 into a new CLB.

The NIH plans to submit a proposed redirection of $60.4 million of existing funds to allow design to begin in the spring of 1995. An additional $32.7 million is requested in FY 1996 to complete the construction of the CLB. The total cost of design and construction of the CLB is $93.1 million.

The current intent is to build the Consolidated Laboratory Building (CLB) as a new, modern, flexible research facility to replace programs in Buildings 2, 3, 7 and the 18/32 temporary complex. It will comprise approximately 248,000 gross square feet of research space and will house about 563 research staff currently on campus. This replacement facility will provide some decompression of currently overcrowded laboratories to create safe, modern research conditions and will replace the temporary laboratory modules which are also located on the campus.

Modern research buildings are typically about 50 percent efficient due to the extensive need for support space to assure the safe function of the facility. To replace the net usable program space in Buildings 2, 3, 7 and 18/32 would require about 238,000 GSF at 50 percent efficiency. The remaining 10,000 GSF provides 5,000 NSF needed as a design reserve to assure that the scientific programs can be adequately supported in the facility.

The new CLB would be located in an existing parking lot bordered by South Drive to the North, Center Drive to the East, Building 12 to the South and Building 13 to the West.

The project is divided into two construction phases. Phase 1 is site and foundations which would begin 18 months after design is started and would take nine months to complete. When Phase 1 is completed, Phase 2, the superstructure, enclosure and fit-out, will begin and be completed 24 months later. Total time from start of design to completion of construction is scheduled to be 51 months. If design is started in the spring of 1995, the project will be completed in the fall of 1999.

Buildings 2 and 3 would be converted into office space, in concert with the recommendations of the U.S. Army Corps of Engineers review committee and appropriately for their historic nature. Building 7 would be demolished along with Building 9. The 18/32 complex facilities are only temporary structures. The funding for these conversions and demolitions are separate from the CLB.

Institutes which would be anticipated to use the space in the CLB include NHLBI, NIAID, NICHD and NCHGR.

There is approximately 2,000,000 NSF of research lab space on the NIH campus. The research space in the CLB is already included and is approximately five percent of this total.

CONSTRUCTION FUND

Mr. Porter: For the future, have you considered establishing a construction fund through regular contributions so that you could avoid large increases in your facilities requests when specific projects need to be funded?

Dr. Kirschstein: Yes, we have considered this approach to funding our B&F projects, but NIH believes it could be difficult to justify the requested funding. Our annual B&F requirements vary considerably and, according to OMB, must be based upon approved program space needs.

Mr. Porter: Would a freeze on the General Services Administration building fund (as has been suggested by the House Budget Committee) have any effect on your ability to pursue these two construction projects?

Dr. Kirschstein: No, we do not use the General Services Administration building fund for funding our buildings.

FIRE STATION

Mr. Porter: Your 1996 budget request includes $5.57 million for a new fire station. Why does NIH have its own fire protection equipment and facility; doesn't Montgomery County provide fire protection services for the campus?

Dr. Kirschstein: The size and complexity of the NIH dictates that the NIH maintain its own capability to manage emergencies that may occur at the Bethesda campus. The research programs of the NIH involve the use of a broad range of chemicals of varying hazard potential, biohazardous agents and/or radioactive materials. Management of emergencies that may involve these materials requires that the NIH have the specialized expertise and equipment immediately available to protect patients, scientists, employees and visitors, and the research laboratory resources and experiments on campus, much of which are not replaceable. Under a Mutual Aid Agreement, Montgomery County Fire and Rescue Service does respond on an as-needed basis to assist the NIH Fire Department, and NIH in turn assists the County on an as needed basis.

Mr. Porter: Identify the anticipated lifetime costs of the various projects proposed for funding in your 1996 Buildings and Facilities request.

Dr. Kirschstein: Lifetime costs are generally defined as costs to maintain and operate a facility over its expected service life. This information is provided for those projects for which this is appropriate.

Estimated Lifetime Costs
(Dollars in Millions)

Project	Facility Life	Design/ Constr. Cost.	Maint.	Util.	Total
Clinical Center	35 years	$380	$126	$497	$1,003
New Fire Station	50 years	6	5	7	18
Consol. Lab Bldg.	30 years	93	30	128	251
NIEHS Add.to Facs	30 years	70	11	35	116

UNCOMMITTED UNOBLIGATED BALANCE

Mr. Porter: What is the current unobligated balance in the Buildings and Facilities account from prior year funding that remains uncommitted for particular projects?

Dr. Kirschstein: The current Buildings and Facilities unobligated balance that remains uncommitted is $114.5 million. The NIH plans to propose a redirection of $60.4 million of these funds to support the design and initial construction of the Consolidated Laboratory Building (CLB). The FY 1996 request includes $32.723 million to complete the CLB construction.

WOMEN'S HEALTH INITIATIVE

Mr. Porter. You have indicated that the Women's Health Initiative is on time and on budget. Can you describe the schedule for recruiting women into the clinical trial and the observational study?

Dr. Kirschstein. The schedule for recruitment of women into the clinical trial and observational study calls for randomization of 64,500 women in the clinical trial and enrollment of 100,000 women in the observational study to be completed by February 1998. To accomplish this schedule, each clinic, both the 16 Vanguard Clinics and the 24 additional clinics, has a goal for recruitment that is set out across the timeline for recruitment. We have a very facile data collection system that permits recruitment to be monitored weekly and we can identify problems or delays at each clinic and deal with them immediately. This has worked well over the past year with the 16 Vanguard Clinics and we expect the 24 additional clinics to make similar progress. These new clinics were to begin recruitment by March 1 and 23 of 24 met that target date; the remaining clinic has now initiated recruitment. The recruitment and follow-up of such a large cohort is a formidable task, the largest ever undertaken, but we have confidence in the investigators, the monitoring system, the NIH staff, and, most importantly, the interest of women in joining the study. Thus far, the experience merits this confidence.

Mr. Porter. When will the community prevention study get underway?

Dr. Kirschstein. We expect the community prevention study to begin in the fall of 1995. The community prevention study has undergone many planning changes, the result of similar studies have been reporting their experience and of changes that have occurred in the general population without community intervention. We did not want to start a study without using the experience of COMMIT and the Stanford and Minnesota studies. It also became apparent that we could develop more effective approaches working in concert with established programs. Recently, we discussed cross-agency collaboration in community prevention with the Centers for Disease Control and Prevention (CDC). Joining the resources and experience of CDC and of the Women's Health Initiative and NIH will yield a better community prevention study (CPS). Therefore, the CPS will be conducted through the CDC Prevention Center Program with oversight by NIH and WHI staff. This program has prevention centers in 16 sites, and the majority are sites with access to and ongoing programs in minority communities, the focus of the WHI community studies. These centers are supported by CDC and NIH will provide funds for specific projects to be carried out in the centers. WHI staff are working jointly with the CDC staff to define these prevention initiatives that will be targeted toward minorities. The initiatives will be announced to the CDC centers in April and they will respond by June. After review by CDC and NIH the initiatives will be funded in August or September and will begin in October. This collaborative effort is an effective and efficient approach to carrying out the goals of the WHI Community Prevention Study.

Mr. Porter. With such a long project [15 years], do you run the risk that the relevant research questions will have changed by the time the Women's Health Initiative is complete?

Dr. Kirschstein. There is always some risk that the burning question of today will be a dying ember tomorrow. However, this risk is minimal for the WHI. The questions being pursued in the clinical trial are large and important and have been asked for 20 or 30 years, but never comprehensively addressed. For example, the effect of a low fat dietary pattern on women's cancers, or, in fat on men's cancers has been the subject of discussion for 20 years but has never been the subject of a trial sufficiently large to answer the question. No other studies are planned or underway anywhere in the world that would answer this important question. The WHI is a clinical trial of sufficient size to unambiguously find an answer. Also, it will describe the effect on heart disease of a diet pattern that may prevent breast and colon/rectal cancer. The implication is that a single dietary pattern could effectively prevent both conditions. This issue has never been addressed. The hormonal replacement study will provide the first clear long-term assessment of benefits and risks when taken as a preventive approach during the menopausal years. Estrogen therapy for menopausal symptoms was introduced over 40 years ago, but there has never been a randomized controlled trial of hormonal therapy that was of sufficient size and duration to provide the benefit/risk information that women need to make decisions about use. WHI will provide that information. Also, biological samples are being obtained and stored from all 164,500 participants in the clinical trial and observational study. Over time, these samples can be analyzed by new, as yet undiscovered techniques. Since all of these women will be followed and many will experience disease and disability, this will permit a search for associations with disease risk and with markers of occult disease. This approach allows for improvement of technologies and for evolving questions of associations. Many of these cannot be anticipated today but will be important tomorrow. In summary, the WHI will test questions that have major public health significance, but are unanswered and yet the study will be able to adapt to changing technologies and questions.

Mr. Porter. Identify the total projected cost of the Women's Initiative by year?

Dr. Kirschstein. The total projected cost for the WHI on a year by year basis is given below:

Women's Health Initiative
Spending Timeframe
(Dollars in Millions)

YEAR	AMOUNT
1992	$22.9
1993	41.1
1994	59.1
1995	57.0
1996	56.8
1997	57.1
1998	54.2
1999	50.7
2000	48.0
2001	50.1
2002	45.0
2003	37.0
2004	36.8
2005	6.6
2006	5.6
	$628.0

DIVERSITY

Mr. Porter. You make reference in your statement to the potential conflict between downsizing and efforts to maintain diversity. What steps are you taking to ensure that personnel reductions don't undercut the progress you have made in promoting minorities?

Dr. Kirschstein. The NIH is actively engaged in a two-track process regarding the direction of its Equal Employment Opportunity (EEO) Program. One track is the critical examination and evaluation of various affirmative action and special emphasis programs. This examination is a part of our streamlining effort and it is intended to ensure more efficient utilization of NIH staff and fiscal resources in this period of budget constraints and government. The second track is the development of a new affirmative action planning process that balances the competing interests of diversity and downsizing. The NIH is committed to diversity and we are approaching it in a way that we believe best recognizes the rights and responsibilities of all employees.

We are also focusing on two major areas which include: developing an Affirmative Action Planning Model that effectively integrates ICDs diversity goals and the streamlined environment while placing greater accountability on the ICDs; and planning an initiative to promote the concept of managing diversity through training and education of the NIH workforce, particularly management officials.

OFFICE OF ALTERNATIVE MEDICINE

Mr. Porter. The Office of Alternative Medicine went through a rocky start-up. With a new director, have some of the problems been resolved?

Dr. Kirschstein. Many of the residual problems from the start up of the office have now been resolved or are in the process of being resolved. A mechanism to provide information services has been set in place through an interagency agreement with the U.S. Army Corps of Engineers. This will facilitate better and faster responses from the OAM to professionals and the public, the Department, the rest of NIH, and to Congress. This will also lay the groundwork for the clearinghouse mandated by Congress as well as other essential components of OAM's information infrastructure. Two major centers have been funded to render technical assistance and perform investigations on alternative therapies for HIV/AIDS, substance abuse and related disorders. Dr. Alan Trachtenberg, the Acting Director of OAM, has brought NIH staff into the office on detail with the requisite expertise to accomplish the office's mission while adhering to NIH procedures and government regulations. Many previous irregularities in office operations have now been resolved and the new permanent director, Dr. Wayne Jonas, will find a smoothly functioning office when he begins his tour of duty in July.

Mr. Porter. Have the issues relating to standards for data collection in grant applications been worked out?

Dr. Kirschstein. The OAM has developed a preliminary set of guidelines for individual clinicians and researchers to follow and begin to interact with program staff in the submission of grant applications and requests for Field Investigations. For the latter, a standard questionnaire has been developed which is sent out to all persons requesting OAM assistance with a field investigation. These mechanisms will help delineate and develop certain ideas regarding the research and use of alternative treatments. At present this program does not involve the set aside of money except for possible technical assistance through the use of consultants.

The "grant application" process in the office includes a separate program, utilizing a peer-review, National Research Service Award post-doctoral training mechanism with subsequent salary support for funded applicants. In addition, persons who wish to apply for grant funding for alternative therapy research outside of the centers program described above have been invited to submit applications in the usual way to the Division of Research Grants (DRG), but to also submit a copy to the OAM, so that OAM can advise DRG on reviewers or consultants who have the needed expertise to review the applications fairly. This will also enable OAM to track the progress of such applications as they are assigned to the appropriate institutes.

TRANSFER AUTHORITY

Mr. Porter. How do you plan to use the Director's one percent transfer authority and the Director's discretionary fund in 1995?

Dr. Kirschstein. A proposal to use the Director's one percent transfer authority in FY 1995 is currently under development; we hope to forward it to the appropriate Committees shortly.

Of the approximately $7.5 million available in the Director's Discretionary Fund in FY 1995, $5 million has been reserved for the James A. Shannon Award Program. An additional $300,000 has been reserved for initiatives of the new Director of the National Institute on Nursing Research. The remaining $2.2 million will be used for high priority initiatives to be determined at a later date.

WOMEN'S HEALTH CURRICULUM

Mr. Porter. The 1995 House report expressed concern regarding the development of a model women's health curriculum for health professions schools and the training of women for leadership positions in medical education. How are you responding to this report language?

Dr. Kirschstein. The ORWH has been actively addressing the mandates of determining the current content of women's health in the medical school curriculum and developing a model curriculum for women's health in health professional education. These efforts have been in conjunction with the Health Resources and Services Administration (HRSA) and in collaboration with the Public Health Service Office of Women's Health.

A preliminary report was submitted in July 1993, and a more recent report was submitted to the Committee in March 1995.

In summary, the Association of American Medical Colleges (AAMC) has undertaken the responsibility of conducting both a preliminary and, now, a more comprehensive survey of the content of women's health in the curriculum. The AAMC has made these data available to us, and ORWH/NIH and HRSA are providing the support for the compilation and analysis of these data for a report to the Congress. It is expected that most of the surveys will have been submitted by early April, and that our analysis will be completed for this report by early to mid May, allowing us to prepare a final report by the end of May.

In conjunction with this activity, work supported by the ORWH/NIH and HRSA, has been ongoing in both developing a model curriculum for women's health as well as identifying current curricula and training models for women's health. This report is in its final stages of preparation, and is expected to be ready for submission to Congress along with the curriculum survey by the end of May. ORWH sponsored a public hearing and workshop to determine barriers and to develop recommended strategies for the recruitment, retention, re-entry and advancement of women in biomedical careers. The report from this workshop was recently published, and has been widely distributed and requested as guidance on advancing career opportunities for women in biomedical careers. This report has been presented to numerous organizations, institutions, and groups who are considering these recommendations to advance careers for women.

In response to the recommendations from this report and the Task Force which heralded this process, ORWH has initiated several programs and opportunities for women to advance in medical and scientific careers. One of these is the ORWH Pilot Re-entry Program for Extramural Scientists, a program which encourages fully trained women (and men) to reenter an active research career after taking time off because of family responsibilities; fifteen reentry supplements have been awarded thus far. This pilot program is now trans-NIH and supported by 16 ICD's. A corresponding intramural program is in place with 3 scientists in NIH labs.

ORWH has also supported and participated in several other programs to encourage the recruitment or mentoring of women into medical or research careers, including science enrichment programs for students and teachers and programs to encourage participation of underrepresented populations such as women and minorities. ORWH also has convened, in conjunction with the NIH EEO Office, a brown bag luncheon seminar to facilitate activities in support of women scientists at the NIH.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAMS

Mr. Stokes. The NIH Revitalization Act of 1993 authorized Loan Repayment and Scholarship Programs including the authorization of the Clinical Research Loan Repayment Program for individuals from disadvantaged backgrounds. Would you update the Committee on this initiative?

Dr. Kirschstein. Based on the NIH Revitalization Act of 1993 which added Section 487E to the PHS Act (42 U.S.C. 288-5), the NIH implemented the Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (CR-LRP) in FY 1994. The CR-LRP has awarded five clinical researchers from disadvantaged backgrounds two-year contracts to conduct clinical research as employees of the NIH. Like the NIH's AIDS Research Loan Repayment Program (AIDS-LRP), which began in FY 1990, the CR-LRP pays a maximum of $20,000 annually in loan repayments to awardees' qualified educational loans.

Mr. Stokes. Also, I understand that a technical correction is needed to make this program consistent with the other PHS Loan Repayment Programs. Would you explain the problem, why it exists, and is the Administration proposing a technical correction?

Dr. Kirschstein. Unlike the AIDS-LRP and the loan repayment programs of the HRSA's National Health Service Corps (NHSC), CR-LRP contract recipients are not able to receive Federal, State, or local tax liability reimbursements. Under Section 338B of the PHS Act (42 U.S.C. 2541-1), the NHSC LRP must provide Federal tax liability reimbursements in the amount of 39 percent of the total loan repayments made and may provide additional State/local tax liability reimbursements. Section 487A (42 U.S.C. 288-1), which authorizes the NIH's AIDS-LRP, states that all the provisions of the NHSC LRP in Section 338 shall also apply, except where inconsistent. Thus, the AIDS-LRP must also provide Federal tax reimbursements and may provide State/local tax reimbursements. However, Section 487E, which describes the CR-LRP, states that only the provisions of Sections 338C and 338E shall apply, except where inconsistent. Since Section 487E lacks the provision for applying 338B, the NIH is unable to extend any tax liability reimbursements to beneficiaries of the CR-LRP.

The LRPs authorized for all other PHS agencies include provisions for tax reimbursements. Additionally, the other LRPs authorized in the NIH Revitalization Act, the General Research LRP and the Contraceptive/Infertility Research LRP (Sections 487B and C), also offer tax reimbursements. The omission of such benefits from the CR-LRP is clearly an oversight and would not appear to be the deliberate Congressional intent to treat recipients of this program in a manner different from all other PHS loan repayment programs. The inclusion of tax reimbursement benefits for this program will be funded from existing appropriated funds, and thus, no additional appropriation is necessary to extend this benefit.

In developing proposals for the reauthorization of NIH for FY 1997, the NIH will be reviewing and considering this issue.

INDIRECT COST

Mr. Stokes. As you know the level of and the variations among Institutes in indirect cost has remained a major concern for the Committee, would you update the Committee on the results of the Indirect Cost Review?

Dr. Kirschstein. Concurrent with the transmittal to Congress of the FY 1996 President's Budget, the Administration published in the Federal Register a series of proposed changes to OMB Circular A-21, "Cost Principles for Educational Institutions." NIH and HHS participated in the development of these proposals through the Committee on Fundamental Science of the National Science and Technology Council. Specifically, the proposed changes include requiring all Federal funding agencies to apply the indirect cost rates in use at the time of the grant award to the life of the agreement, which would ensure more consistency across Federal agencies and more accurate predication of outyear costs. The determination of indirect cost rates would be made more consistent by changes such as eliminating special studies used by many institutions to allocate certain facilities costs to Federal research, as well as be developing appropriate criteria for the reimbursement of interest costs.

Other proposed changes would clarify the policy governing the calculation of indirect cost rates related to facilities and other assets during an institution's transition from use allowance methods to depreciation; eliminate the allocability of dependent tuition benefits; and formally modify the terminology of "indirect costs" in the A-21 Circular to "facilities costs and administrative costs" to be more sufficiently descriptive.

OMB also proposes to develop processes in the near future that would benchmark the costs of facilities construction and acquisition and utilities, and treat specialized services and facilities more uniformly. Data necessary to assess the consistent treatment of the costs of building and operating specialized use facilities is currently under development.

Mr. Stokes. How wide of disparity have you seen in indirect cost among institutions and to what is it attributed?

Dr. Kirschstein. Indirect cost rates ranged from 33 to 79 percent modified total direct costs in FY 95, with a weighted average among high volume institutions of 50.5 percent. There are many other less research intensive institutions with lower salary and wage based indirect cost rates. While it is difficult to explain all of the variance among institutions, some of the range is due to differences between public and private institutions, region of the country, and magnitude of the research operation. Additional differences in costs are likely to occur because of the range of sophistication of specialized facilities, age of the physical plant, and so forth.

Mr. Stokes. To what extent is indirect cost used to strengthen the infrastructure at these institutions?

Dr. Kirschstein. Indireot costs are not used to strengthen the physical plant per se. Rather they are paid as reimbursement to institutions for expenditures that have already been incurred for operations and maintenance and the depreciation or use of the actual research space. While depreciation charges include whatever costs may have been incurred for recent construction and renovation, by far the majority of the costs are for long-standing research facilities and equipment. Depreciation charges for research space represent approximately eight percentage points of the average overall rate of approximately 52 percent.

Mr. Stokes. What is the Level of indirect cost at the HBCUs and other primary minority serving institutions?

Dr. Kirschstein. Indirect cost rates for representative sample of Historically Black Colleges and Universities (HBCUs) range from 33 to 63 percent modified total direct costs. There are also quite a few of the less research intensive HBCU institutions which have lower salary and wage based rates. This range of rates is not unlike other universities of the same approximate level of research intensity.

OUTCOMES FOR RESEARCH GRANT APPLICATIONS

Mr. Stokes. According to the Congressional Justification, in follow up to House Report Language last year concerning the outcome of those researchers who are unsuccessful in applying for NIH grants, the NIH conducted a review of the Fiscal Year 1990 cohort of applicants for research grants. The justification indications that the analysis revealed that 71 percent of the original applicants for funding in FY 1990 received some type of independent research support from the NIH by the end of 1993. What was the percentage experienced by women and minority researchers in this cohort analysis?

Dr. Kirschstein. Based on the study of fiscal year 1990 Cohorts and the analysis that revealed that 61 percent of the original applicants received some type of independent research support from NIH, the following statistics indicate the percentage experienced by women and minorities: 1) Of all those awardees that had indicated their gender, 19 percent were women; and 2) Those that indicated their ethnicity, 11 percent were minorities (American Indian or Alaskan Native, Asian or Pacific Islander, Black, and Hispanic).

Mr. Stokes. The justification goes on to state that it is very likely that some portion of the remaining 29 percent of the applicants received support from staff positions on NIH research grants and from other federal and non-federal sources. What was the likelihood for this alternate source of funding to have been provided for women and minority researchers?

Dr. Kirschstein. Information on staff positions is not collected centrally and therefore is not available.

ORMH PILOT PROJECTS

Mr. Stokes. To what extent have ORMH Pilot Projects that have proven to be successful been fully adopted for funding support by the Institutes, Centers, and Division of the NIH?

Dr. Kirschstein. Two types of collaborations occur between the Office of Research on Minority Health (ORMH) and the Institutes, Centers, and Divisions (ICDs). The more common scenario is for the ORMH to utilize funds appropriated to the Minority Health Initiative (MHI) to support new minority health research programs completely during their pilot stages. However, in some cases, ORMH/MHI funds are leveraged through equal cost-sharing with the partner ICD from the outset. Notably, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has been a full partner with the ORMH, bearing an equal share of the cost of new joint programs, including several research projects focusing on diabetes prevention in minority populations.

Because many of the research projects supported through the MHI are long-term in nature, and because the initiative is now only in its third fiscal year, there has been insufficient time to reach definitive conclusions about the success of many MHI-supported programs. However, the ORMH has developed a transition plan whereby ORMH/MHI funding of projects deemed successful will be phased out over a 2-year period and financial responsibility for the projects' continuation will be transferred to the relevant ICD. The ICDs are fully aware of their responsibilities under this transition plan.

The ORMH is currently in the process of implementing a comprehensive prospective evaluation system that will assess the effectiveness of all NIH minority research and training programs. The evaluation system will be fully implemented by the end of FY 1996. At that time, ORMH will have the necessary information to determine program effectiveness. Programs deemed ineffective will be abandoned, while those that have demonstrated success will be transferred to the ICDs under the terms of the transition plan.

Mr. Stokes. Last year, the office indicated that it would be updating its original Fact Finding Report. What is the status of the addendum?

Dr. Kirschstein. As a follow-up to the 1991 consultative effort that resulted in the Fact-Finding Team (FFT) report, the ORMH convened the National Conference on Minority Health Research and Research Training in Chicago, Illinois, on March 27-30, 1994. The conference developed new recommendations from the minority community intended to provide guidance on the direction of ORMH programs for the period 1995-2000.

The consensus of the participants, as expressed in their responses to a Conference evaluation questionnaire, was (1) that ORMH personnel have been receptive to input from the community; (2) that the ORMH has made good progress in generating programs responsive to the original 13 FFT recommendations for minority health research and training; and (3) that the ORMH has increased awareness of minority concerns at all levels of the NIH. The participants agreed that the ORMH should continue to encourage NIH ICDs to fund more minority research and to collaborate with other government agencies to leverage funds dedicated to minority programs. Over three-quarters of the Conference participants felt that the ORMH is achieving its dual goals of increasing research on diseases affecting minority groups and involving more minorities in biomedical research.

The participants expressed strong support for the continued pursuit of the original 13 FFT recommendations. It recommended additional efforts in the areas of behavioral and social science research, infrastructure development, data collection and dissemination, community outreach, and collaboration with governmental and nongovernmental entities. The participants emphasized that the ORMH should function as a strong trans-NIH office with responsibility for the coordination and review of all NIH minority health and training programs. To assist the ORMH in the development of its programmatic initiatives, the participants recommended the formation of an external Advisory Committee. A report of the conference proceedings and recommendations is currently under development.

AIDS RESEARCH

Mr. Stokes. How are priorities established for the AIDs research, research training, and outreach, and also, how are funding levels for the various NIH components established?

Dr. Kirschstein. In order to establish priorities for AIDS research, research training and outreach, the Office of AIDs Research (OAR) prepared a comprehensive plan through a unique and inclusive mechanism that will serve as the model for the annual OAR planning process. Five Coordinating Committees, consisting of NIH staff members were established to develop plans for specific areas of AIDS/HIV research: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral Research. The members of the Coordinating Committees were selected by the OAR from the staff of those NIH ICDs with the most significant research portfolios in the scientific areas. The Coordinating Committees developed the first draft of the FY 1996 Plan addressing the process strictly from the perspective of the priorities of the overall scientific area, not from an ICD-specific perspective. The draft plan developed by the Coordinating Committees was then sent to each ICD Director and ICD AIDS Coordinator. Their recommendations and suggested additions or changes were appended to the plan.

A large workshop was then held to review and revise the draft plan. In addition to ICD Directors, AIDS Coordinators, and NIH

Coordinating Committee members, attendees at this workshop included invited experts from universities, research institutes and industry, and representatives of community organizations. Meeting in working groups for each of the areas of emphasis, these NIH scientists, nongovernment researchers, and other experts worked together to form a consensus regarding the formulation and prioritization of the scientific objectives within each area of emphasis. These groups also developed more specific strategies to illustrate the types of research that would aid in attaining the goals envisaged within the specific objectives.

Following the workshop, a small group of eminent scientists was convened, including the Director and Deputy Director of the NIH, to review the plan and to assist OAR in establishing priorities across the broad areas of science. The plan was then presented to the AIDS Program Advisory Committee (APAC), a group of experts representing a wide breadth expertise and experience, who provide guidance to the Director of OAR and the Director of NIH. The APAC, which had discussed the document on a number of occasions throughout its development, gave final approval to the plan. This planning process resulted in an unprecedented consensus regarding the goals and directions required to move AIDS research forward.

Proposed funding levels for the NIH ICDs were established based on this plan. ICDs submitted proposed budgets to the OAR, detailing projects which would best take advantage of the scientific opportunities and priorities of the plan. These submissions underwent intense review by the OAR Director and staff. For funding to the various NIH components above the commitment base, the following criteria were considered in reviewing each project: relevance to the priorities of the plan, the urgent need to pursue available scientific opportunities; commitment to supporting only the highest quality research; and the necessity to eliminate unnecessary duplication and overlap of efforts and to coordinate research activities among the ICDs.

Mr. Stokes. In response to the provisions contained in the Revitalization Act of 1993, the FY 1996 budget continues to include all AIDs and related funds in a single appropriation account for the Office of AIDs Research. In your professional judgement, how well is this approach working?

Dr. Kirschstein. Last year was the first year that the single line item mechanism was in place. The OAR carried out its obligation to transfer the funds to the ICDs well within the required time limits. The Congressional appropriation was less than the President's request in FY 1995; hence the single appropriation process allowed the OAR to determine the appropriate shift in funds to ICDs, based on scientific opportunities set forth in the comprehensive plan. The single appropriation allows the OAR to preserve support for the highest priority scientific areas, as outlined in the OAR's comprehensive plan. In addition, the single appropriation allows the Director of OAR to bring about the redirection of research across all of the institutes. The previous system did not lead to effective coordination of the research effort, and it would have been even less effective in refocusing those efforts. Thus, the single appropriation is essential for better management and scientific oversight of the vast HIV/AIDS research effort at the NIH, particularly in a time of fiscal constraint.

Mr. Stokes. Are there specific concerns with regard to this approach?

Dr. Kirschstein. The NIH feels this system is working well and has no concerns about continuing the single appropriation.

MINORITIES AND WOMEN IN CLINICAL TRIALS

Mr. Stokes. Would you update the Committee on the progress that is being made with respect to increasing the participation of minorities and women in clinical trials?

Dr. Kirschstein. It is NIH policy that members of minority groups be included as subjects in all NIH-supported clinical research projects, unless there are compelling reasons why such inclusion is inappropriate. Minorities should be included in research study populations to (1) prevent exclusion of any racial or ethnic group without rational basis; (2) make study results more representative of the entire population; and (3) begin the identification of differences that may exist in the response of minority individuals to drugs and other forms of treatment.

In the past, some research studies that included minorities were of poor scientific quality and involved abuse or mistreatment of participants. These unfortunate experiences, along with economic disadvantage and other factors, combined to make many minority individuals reluctant to take part in clinical research. Therefore, while there is a need to include more minorities in research study populations in order to answer important scientific questions, there is also a need to design studies with sensitivity to overcome the reluctance of many minority individuals to participate in clinical research. ORMH is working in partnership with the ICDs of NIH, as well as other Public Health Service agencies, to meet the challenge through collaborative research projects developed in consultation with a broad cross-section of organizations representing minority communities.

During 1996, ORMH will sponsor meetings and presentations in the research and minority communities to demonstrate to biomedical researchers that (1) including minorities in studies will improve results and (2) minority subjects can be recruited to participate in biomedical studies; as well as to demonstrate to minority groups the value of participating in biomedical studies and to facilitate communications among researchers and minority community health organizations.

The Office of Research on Women's Health (ORWH), in conjunction with the ORMH, the Office of Extramural Research, and the Office of

Intramural Research, has taken many steps to increase the participation of women and minorities in clinical trials. Our inclusion policies were revised and strengthened in response to the NIH Revitalization Act of 1993, and new guidelines were published in the Federal Register on March 28, 1994 with a one year public comment period. After publication of the NIH Inclusion Guidelines, extensive training on the revised policy was conducted for both extramural and intramural staff. Training materials for inclusion were developed and widely distributed, and are available from the ORWH. Scientific Review Administrators are continuing to instruct reviewers and applicants about the revised policy, and to ensure that inclusion is considered as one of the criteria of scientific merit.

ORWH conducted a major public hearing and workshop to address barriers to participation by women and minorities and have released a report of this workshop, entitled Recruitment and Retention of Women in Clinical Studies. In addition, NIH published an Outreach Notebook to further assist researchers with recruitment and retention of women and minorities. Both documents were widely distributed within NIH and to organizations and individuals in the extramural scientific community. We have also been proactive in numerous outreach efforts by participating in public forums and workshops to explain, encourage, and familiarize researchers, as well as women and minorities, about the need for inclusion in clinical trials. NIH representatives have presented at numerous national and regional meetings, such as those conducted by the Office of Protection from Research Risks (OPRR), the House of Delegates of the American Medical Association and the National Medical Association, the American Medical Women's Association, the Society of Behavioral Medicine, Public Responsibility in Medical Research (PRIM&R), the Applied Research Ethics National Association (ARENA), and many academic and community groups. To further encourage the inclusion of groups who have been underrepresented in clinical trials in the past, ORWH has initiated a supplemental grant program to expand the participation of women and minorities in research studies in areas such as breast cancer, AIDS, diabetes, hypertension or to develop innovative ways to enhance recruitment.

We have just reached the end of the one-year public comment period for the revised Inclusion Guidelines and analysis of the responses has begun. Institutes and Centers (Ics) continue to collect data and monitor compliance by grant awardees. In response to the Revitalization Act's requirement to monitor the inclusion of women and minorities, ORWH is presently refining existing mechanisms to facilitate tracking the number of subjects in clinical research studies throughout the NIH. ORWH staff chair a coordinating committee to overseeing implementation of the inclusion policy across the NIH.

OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

Mr. Stokes. In testimony before the Subcommittee, the Heritage Foundation recommended the elimination of the Office of Behavioral and Social Sciences Research. However, when the Committee had the opportunity to hear testimony from six of the nation's nobel laureates, they indicated that behavioral research was one of the most important areas that if enhanced -- offered considerable opportunity for furthering medical advances and for improving Americans' health status. My question is what makes this area of research a prime investment, and is the mission of the Office of Behavioral and Social Sciences Research no longer viable?

Dr. Kirschstein. Scientists now recognize the enormous impact of behavior on human health and disease. New knowledge gained through behavioral and social sciences research is indispensable for understanding how individual, familial, social, and environmental factors interact with biological factors to contribute to the promotion of health and the prevention of disease and disability.

This Office will provide the infrastructure to promote new inquiry in the area of health and behavior, to help establish meaningful research goals, and to integrate the NIH-wide effort. The mission is viable and reflects the NIH's continuing interest in helping the American people attain the highest possible level of personal health.

Mr. Stokes. What is the extent of the NIH's investment in this particular area of research in FY 1996?

Dr. Kirschstein. Health and Behavioral Research is an integral part of the NIH research portfolio. Each Institute and Center, including the three Institutes that rejoined the NIH from the Alcohol, Drug Abuse and Mental Health Administration, has developed a plan with projected commitments. In FY 1996 it is estimated that $819,000,000 will be used to support projects that contain a behavioral research component. The 1996 estimate represents a modest increase in support for this effort. Specifically for the Office of Behavioral and Social Sciences Research (OBSSR), the FY 1996 budget request is $2,363,000.

Mr. Stokes. How does this compare with the funding level for FY 1995 and 1994?

Dr. Kirschstein. The following figures are actual and planned investments in projects that contain a behavioral research component: FY 1994 - $776,000,000; and FY 1995 - $798,000,000. The OBSSR was funded at $2,240,000 in FY 1995.

MINORITY HEALTH

Mr. Stokes. As I am sure you are aware, the disparity in minority health continues. While this issue is complex and a multiplicity of factors contribute to the disparity including life style and access to health care, biomedical research does have a key role to play in helping to close the gap. With respect to the leading causes of excess deaths in minorities, what are the major areas of emphases for the Office of Research on Minority Health under the FY 1996 Budget Request level?

Dr. Kirschstein. The MHI's FY 1996 Budget Request Level is $62.8 million, which will support a series of multi-year research studies designed to shed light on some of the most important disparities in minority health status. The MHI has five components that address significant minority health issues across the lifespan. The Initiative is administered by the ORMH and the research studies are managed by the component Institutes of NIH in partnership with the ORMH.

The Infant Mortality component of the MHI supports community-based epidemiological and clinical research to address the problem of the unacceptably high infant mortality rate in Washington, D.C. Despite overall improvements in national infant mortality rates, African American infants continue to be twice as likely as white infants to die within the first year of life. This problem can clearly be seen in the District of Columbia, a predominantly African American city that has the Nation's highest infant mortality rate.

The Minority Children component focuses on research on injury-related morbidity, lead poisoning, asthma, learning disorders, and hearing and speech impairments among children ages 1-9. This component includes a major research initiative to address the etiology and treatment of a variety of environment-related health problems in minority children.

The Minority Youth Initiative component focuses on evaluating and comparing various community-based interventions to decrease violence-related injuries and deaths, sexually transmitted diseases (STDs), and unintended pregnancies in minority youth ages 10-24. Minority youths are at greater risk for suicide, homicide, substance abuse, unintended pregnancy, and STDs, including AIDS. Homicide is the leading cause of death for minority youth. This initiative also supports a comprehensive community-based program to include minority adolescents with HIV in clinical studies of novel HIV treatments.

The Young Adult Initiative supports a variety of research projects, both intramural and extramural, related to the health problems and behaviors of young minority adults. Research projects focus on minority health problems such as kidney disease, hypertension, diabetes, obesity, glaucoma, hemochromatosis, systemic lupus erythematosus, alcoholism, and AIDS. Studies to examine the recruitment and compliance of minorities in clinical trials are also supported.

The Older Minority Americans component of the MHI funds research centers dedicated to the study of diseases and conditions that lead to ill health and disability in aging minority populations. Six centers are currently studying such conditions as hypertension, cancer, diabetes, and arthritis.

The following are examples of research projects supported under the MHI on particular diseases that cause a disproportionate burden of ill health and disability among minority populations.

Systemic lupus erythematosus (SLE), a painful disease of the immune system that primarily afflicts women, is three times as common among African American women than among white women. The National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS), in partnership with the ORMH/MHI, is supporting basic, clinical, and epidemiological research projects to determine the causes of SLE and to investigate why the disease is more common in women and minorities. Two specialized Centers of Research on SLE have been established to provide additional focus on the problem.

Noninsulin dependent diabetes mellitus (NIDDM) and its complications constitute a major health problem in several minority populations. Hispanic Americans have three times the risk of developing NIDDM as non-Hispanic whites, while Native Americans are 10 times more likely than whites to develop NIDDM. In partnership with the ORMH/MHI, the NIDDK is giving a high priority to research studies aimed at identifying genes and genetic markers associated with NIDDM in minority populations. Thus far, several potentially important genetic markers have been identified in African Americans with NIDDM. Studies of Creole Indians with NIDDM have identified a significant association with a particular gene that is not seen among other Indian subpopulations with NIDDM. These findings are important because the discovery of genetic markers for NIDDM in particular minority groups will allow a more focused effort to understand the underlying mechanisms of this disease so that appropriate treatments may be developed.

Drug Abuse is a significant health problem among minority populations. Minorities are more likely than non-minorities to die as a result of drug abuse, to suffer severe drug-related illness, to receive inadequate treatment, and to be involved in drug-related violent crime. The National Institute on Drug Abuse, supported by the ORMH/MHI, is aggressively engaged in a broad spectrum of research, prevention, treatment, education, and training programs to meet the special needs of minority populations in regard to drug abuse.

Health problems associated with exposure to environmental contamination, including respiratory diseases and lead poisoning, are more common among minorities and low-income groups than among the population as a whole. The National Institute for Environmental Health Sciences (NIEHS), in partnership with ORMH/MHI, has initiated the Developmental Centers Program to support multidisciplinary research centers that utilize state-of-the-art science to address the environment-related health problems of economically disadvantaged and/or underserved populations. The Center for Bioenvironmental Research, a collaborative effort between Tulane University and Xavier University (a historically black institution) is the first such center to be funded. It has begun a clinical trial to study the effects of lead exposure in African American children, as well as studies of the health effects of lead in pregnancy. The National Institute of Allergy and Infectious Diseases (NIAID), in partnership with ORMH/MHI, is supporting studies of asthma in Hispanic and Asian populations.

WOMEN'S HEALTH

Mr. Stokes. With respect to the leading causes of deaths and disabilities in women, what are the major areas of emphasis for the Office of Research on Women's Health and the Women's Health Initiative under the FY 1996 Budget Request Level?

Dr. Kirschstein. The Office of Research on Women's Health (ORWH) will continue to address major causes of death and disability, as well as other factors that affect the quality of life of women. In FY 1996, the ORWH will do a major reanalysis of the research agenda established in 1991, in conjunction with NIH Ics, the ORWH Advisory Committee, other scientists, and advocacy groups.

For FY 1996, ORWH has targeted several areas that will impact on the major causes of death and disability among women. ORWH has begun to develop projects with NIEHS and other Institutes that will examine the relationship between environmental exposures to carcinogens that mimic estrogens and that may result in cancer, autoimmune diseases and/or adverse reproductive conditions. In addition, ORWH will address the legal and ethical implications related to current issues in women's health research, such as the inclusion of women of childbearing age in clinical trials and the scientific, legal, and sociocultural consequences of genetic testing of women. Another area that has devastating consequences for women and their newborns is sexually transmitted disease. ORWH will work with NIAID to develop a research program, building on recent results, to examine and test the process that led to the eradication of chlamydia in some communities. In FY 1995, ORWH began a major project with NIDDK to examine cardiovascular disease among women with diabetes. In FY 1996, we will build upon this project to include the role of genetic and environmental factors in the link between cardiovascular disease and diabetes in women. Other consequences of diabetes in women will be explored as well. ORWH will join with NIAMS to support research that examines the effect of exogenous hormones, such as contraceptives and hormone replacement therapy, on women with autoimmune disease. In addition, ORWH will continue its support of research in the prevention and treatment of disabilities and join with the National Institute on Child Health and Human Development to fund research on fitness among women with physical disabilities.

ORWH will continue to cosponsor, with the National Institute on Aging and the National Institute of Nursing Research, a study of the natural history of menopause. The study will examine changes occurring in the cardiovascular and skeletal systems as women pass through menopause. It will provide new data on menopause and the associated changes among women of diverse ethnic backgrounds including African American, Hispanic, Asian and Caucasian women. ORWH will continue to support activities to ensure strong outreach and recruitment efforts in the diverse communities.

The WHI specifically addresses several of the leading causes of death by testing promising but unproven approaches to prevention of these diseases (clinical trial) and by identifying and quantifying risks (observational study). The clinical trial tests the effect of a low fat dietary pattern on the development of heart disease (leading cause of death for women), breast cancer (most frequent cancer), and colon cancer (third most common cancer). It is likely that information about prevention of diabetes (a leading contributor to death and disability) will also result. The hormonal component of the clinical trial tests the benefits of long-term administration on heart disease and osteoporosis (a leading cause of disability in women) and will help define the risk of breast cancer. The calcium/vitamin D component will test the ability of an inexpensive dietary supplement to decrease osteoporosis and bone fracture and to prevent colon cancer. The effects of these preventive approaches on stroke may also be determined. The observational study will follow a large cohort of older women and determine whether new measurements can predict development of disease or act as markers for disease. Only one of the leading causes of disease for women is not being directly addressed and that is lung cancer. Smoking is the overwhelming preventable cause of lung cancer. The community prevention component will target smoking cessation while maintaining weight and will endeavor to add to the current overall decline in smoking which has not been as rapid as for men.

Mr. Stokes. According to the Congressional Justification for the National Center for Human Genome Research, researchers have found over 40 different mutations of the BRCA-1 Gene. I understand that each of these genes is apparently associated with a dramatically increased risk of breast cancer and/or ovarian cancer. With this valuable knowledge in hand how will it be used to further work in the Women's Health Initiative?

Dr. Kirschstein. The BRCA-1 gene is the underlying alteration in approximately half of early-onset breast and ovarian cancer families which constitute only 5 to 10 percent of all breast and ovarian cancer cases. In excess of 80 different mutations in the BRCA-1 gene have been reported to date. Current technologies can be used to identify individuals at risk for breast and ovarian cancer in high-risk families. Currently the identification of mutations in BRCA-1 families is being carried out in a research setting. Techniques are not available for routinely evaluating the BRCA-1 gene in members of suspected breast cancer families in a clinical setting. These techniques are being developed by commercial companies and may become available within the next year.

The actual level of risk associated with BRCA-1 or other breast cancer susceptibility genes is not presently known. This is because the identification of BRCA-1 has relied upon the characterization of families where most, if not all, individuals carrying a mutant BRCA-1 gene are affected by disease. It is not known whether the BRCA-1 gene plays a significant role in families where breast and ovarian cancers are less frequently observed or in cases of sporadic breast or ovarian cancer. Ongoing studies will elucidate the role of BRCA-1 in these cases.

Additional research has suggested the existence of other susceptibility genes. Current research has identified the location of a second hereditary breast cancer gene, BRCA-2, on chromosome 13. Existence of a "BRCA-3" gene has also been suggested in recent reports. Intensive investigations to identify important genes that are causative in sporadic cancer as well. Detection of these mutations in early stage disease may aid physicians in selection of appropriate therapy for individual patients. The characterization of these genes may result in the identification of new targets for therapy as well.

Information about specific genetic alterations that predispose women to breast and other cancers will enhance the WHI by suggesting additional possible items to be included in both the observational arm and the intervention components. Specimens collected can be used for studies of prevalence of genetic alterations.

Mr. Stokes. Describe the collaborative relationship that the Office of Research on Women's Health and the Women's Health Initiative have with the National Cancer Institute?

Dr. Kirschstein. One of the main components of the WHI is a randomized trial to evaluate the effect of a low-fat dietary pattern on the prevention of breast and colon cancer and coronary heart disease. The clinical study is being conducted at 40 clinical centers located throughout the United States.

The early work on diet was done under the auspices of the National Cancer Institute (NCI). Their efforts included determining the feasibility of having women adhere to the dietary requirements. When the issue arose of adherence for minority populations, whose dietary patterns were different than those initially examined, the NCI conducted pilot feasibility studies in minority communities. These pilot studies refined the intervention for the minority populations, and worked out inconsistencies that allow the full scale trial to occur in multiple clinical settings.

The scientists from the NCI joined with the leaders from the WHI and the ORWH develop the full scale implementation plan. NCI scientists are project officers, provide nutritional expertise, and statistical review for the ongoing trial. Weekly meetings are conducted with the staff from ORWH, WHI and NCI to discuss issues, enhance communication and address problems. This collaboration has resulted in a well balanced scientific and administrative team to manage this trial.

INTRAMURAL RESEARCH

Mr. Stokes. What were the major recommendations contained in the External Advisory Report on the NIH Intramural Research Program?

Dr. Kirschstein. The report of the External Advisory Committee (EAC) on the intramural research program was transmitted to the

Director, NIH, on April 11, 1994. An "Implementation Plan and Progress Report" giving detailed responses to each of the 42 recommendations made in the Report of the EAC was submitted and discussed by the Advisory Committee to the Director, NIH, (ACD) on December 2, 1994. The ACD unanimously approved that implementation plan, and it is currently being printed together with the EAC Report.

Major recommendations of the EAC Report related to acquisition of tenure, review of tenured scientists and Scientific Directors, postdoctoral training, organizational issues affecting recruitment and retention, NIH-private sector collaborations, allocation of funds between intramural and extramural programs, and renewal of the Clinical Center. Most of the changes suggested in the EAC Report have already been addressed by the NIH Director and the Deputy Director for Intramural Research in conjunction with the Institute and Scientific Directors, and other changes are in progress.

Extramural Associates Program

Mr. Stokes. Is there a planned increase for the budget of the Extramural Associates Program?

Dr. Kirschstein. The Extramural Associates Program initiated the Extramural Associates Research Development Award (EARDA) in FY 1994. The purpose of this program is to provide assistance to qualifying minority and women's colleges develop or strengthen offices of sponsored research as a means of becoming more competitive in obtaining NIH research support. In FY 1994 funds were provided in the budget of the Director, NIH for the EARDA program and six awards were made. In FY 1995, nine new awards and six continuations will be supported. For FY 1996 we plan to support eight new awards and 15 continuations.

Fact Finding Team

Mr. Stokes. Given the suggestion of the Fact Finding Team for Office of Research on Minority Health to become the umbrella for all of the Minority programs, are steps being developed for a stronger relationship between the ORMH and the various programs (e.g., MARC, MBRS, RCMI, EA Program, etc.) which support the minority community?

Dr. Kirschstein. The 1991 Fact Finding Team (FFT) recommended that the ORMH coordinate and review all minority NIH programs to eliminate any duplication of effort, to ensure that programs meet overall guidelines, to ensure the general and timely dissemination of research results among the minority communities, and to encourage collaboration between major research institutions and minority institutions.

At present the ORMH functions in a collaborative rather than a coordinating mode. Two types of collaborations occur between the ORMH and the various ICDs. The more common scenario is that the ORMH utilizes funds appropriated to the MHI to provide full support, during their pilot stages for new health research and research training programs for minorities. In some cases, ORMH/MHI funds are leveraged through equal cost-sharing with the partner ICD from the outset. In this manner, the ORMH is able to spearhead new initiatives. The ORMH has also successfully encouraged another collaboration effort, this time between major research institutions and minority institutions such as two major ORMH supported training efforts--The Bridges Program and the Minority International Research Training Program. Other activities that support majority-minority institutional partnerships are: the Developmental Centers Program with the National Institute of Environmental Sciences and the newly announced Research Infrastructure in Minority Institutions Program with the National Center for Research Resources.

Although there is no general coordinating role for the ORMH in terms of oversight of all minority programs, it is our hope that the collaborative approach with the ICDs will eventually lead to a coordinating function for the Office. Such a role would be advantageous by enabling (1) review of the complete minority program portfolio for duplication of effort; (2) more uniform correspondence between the health needs of the community and the NIH program effort; and (3) development of strategies for the evaluation and management of the minority program efforts.

EEO Rating Criteria

Mr. Stokes. Has there been an assessment of the reliability of the EEO rating criteria for senior managers at the NIH to assure that this criteria reflects actual performance in this area? (Note that there have been some suggestions that managers are uniformly rated high on this criteria.)

Dr. Kirschstein. In September 1993, it was determined that the performance reviews of every SES/SSS (senior executive) and PMRS (manager) employee include a discussion of the EEO element. The directive required that written remarks, including specific examples, be developed to show how well the employee met the performance standard. Also it was requested that the Director, OEO, and the Director, Office of Human Resource Management do the following: (1) review a random sample of the final 1993 performance plans for supervisors, managers, and executives across the NIH; (2) determine how well the EEO element was applied; and (3) report the findings.

A committee of 15 NIH officials representing the intramural, extramural, administrative, EEO and personnel communities reviewed a sample of 121 SES/SSS and 333 PMRS ratings. Results of the review indicated, with about 95% certainty, that the percentage of noncompliance regarding SES/SSS EEO elements was between 56% and 66%; the percentage of noncompliance for PMRS EEO elements was between 64% and 74%. The EEO element ratings were considered deficient primarily because the written remarks were not adequately developed, i.e., were too brief or too general, did not address the standards, or justified a rating other than the one assigned.

As a result of the findings and in concert with recommendations of the NIH EEO Executive Advisory Committee, it was suggested that NIH revise the EEO critical elements, develop performance standards at the Fully successful and Excellent levels, and establish ICD Performance Review Boards to review all ratings of outstanding and excellent. The NIH has revised the standards and levels, and each ICD established a Performance Review Board to ensure consistency and accuracy in the 1994 rating process. Results of the 1994 performance review cycle have not yet been analyzed.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

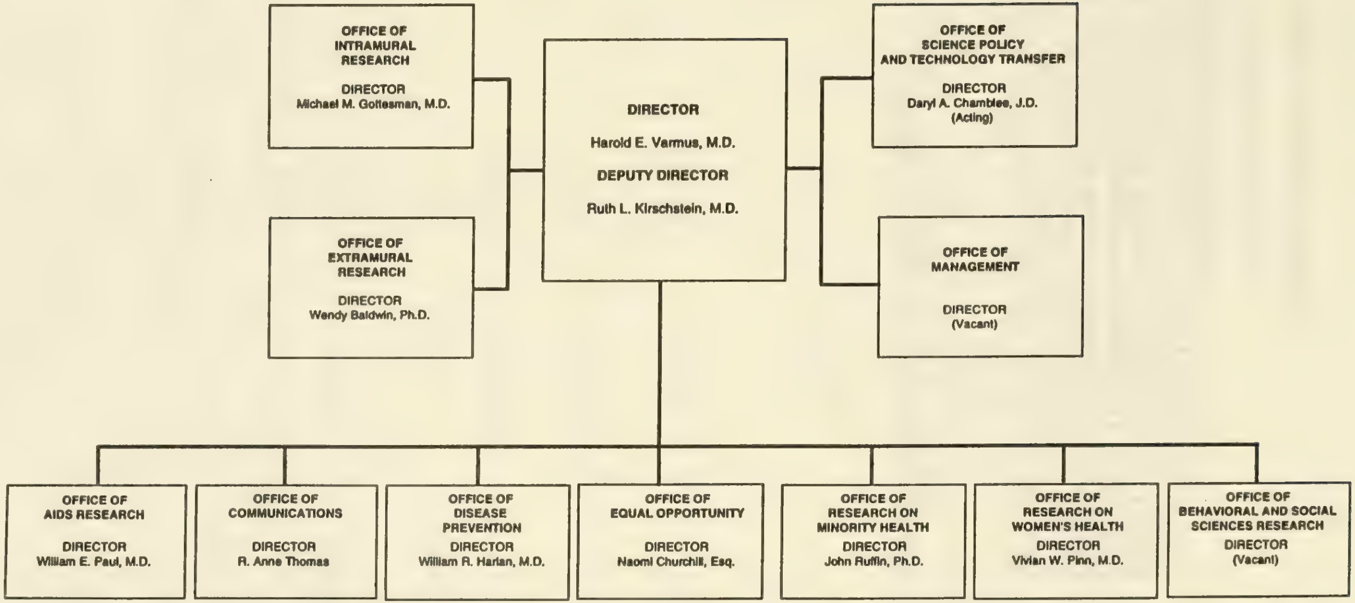
NATIONAL INSTITUTES OF HEALTH

Office of the Director

FY 1996 Budget	Page No.
Organization chart	120
Appropriation language	121
Amounts available for obligation	122
Budget mechanism table	123
Summary of changes	125
Budget authority by object	126
Administrative costs	130
Significant items in House and Senate Appropriations Committee reports	132
Authorizing legislation	146
Appropriation history	147
Budget authority by activity	148
Justification:	
A. General statement	149
B. Research management and support	153
C. Detail of full-time equivalent employment (FTE)	162
D. Detail of end-of-year employment	163

NATIONAL INSTITUTES OF HEALTH

Office of the Director Organization Structure



NATIONAL INSTITUTES OF HEALTH

Office of the Director

For carrying out the responsibilities of the Office of the Director, National Institutes of Health, [$218,367,000 of which $3,375,000 shall be transferred to the National Institute of General Medical Science], *$230,256,000*: Provided, that funding shall be available for the purchase of not to exceed five passenger motor vehicles for replacement only: Provided further, That the Director may direct up to 1 percent of the total amount made available in this Act to all National Institutes of Health appropriations to activities the Director may so designate: Provided further, That no such appropriation shall be increased or decreased by more than 1 percent by any such transfers and that the Congress is promptly notified of the transfer.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation	$233,605,000	$218,367,000	$230,256,000
Rescission in accordance with PL 103-211	-6,415,000	---	---
Section 205 Procurement reduction	---	-185,000	---
Section 513 S&E reduction	---	-253,000	---
Subtotal, Adjusted Appropriation	227,190,000	217,929,000	230,256,000
Real transfer to NIGMS for MARC and MBRS Programs	---	-3,375,000	---
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	-24,538,000	---	---
Comparative transfer to: NIDDK for Nutrition Coordinating Committee	-316,000	-446,000	---
Comparative transfer to: NIDCD for the Deputy Director	-223,000	-215,000	---
Comparative transfer from: NIMH, NIDA, AND NIAAA to OD for accounting	+572,000	+572,000	---
Subtotal, adjusted budget authority	202,685,000	214,465,000	230,256,000
Unobligated balance, lapsing	-146,000	---	---
Total obligations	202,539,000	214,465,000	230,256,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1994 - $52,084,000; FY 1995 - $54,537,000; FY 1996 - $54,534,000.

Also excludes funding for HIV activities: FY 1995 -- $25,394,000; FY 1996 -- $27,598,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research Management & Support....	700	$202,685,000	705	$214,465,000	686	$230,294,000
OD Operations....................	(638)	(42,001,000)	(643)	(45,007,000)	(624)	(47,438,000)
Director's Discretionary Fund....		(6,322,000)		(7,499,000)		(7,499,000)
Laboratory for Diagnostic Radiology Research.............	(9)	(1,997,000)	(9)	(1,910,000)	(9)	(2,015,000)
Office of Alternative Medicine...	(5)	(3,386,000)	(5)	(5,398,000)	(5)	(5,694,000)
Academic Research Enhancement Award Program..................		(13,234,000)		(12,696,000)		(14,092,000)
Science Education................	(4)	(1,813,000)	(4)	(1,795,000)	(4)	(1,893,000)
Research on Minority Health......	(8)	(9,794,000)	(8)	(8,942,000)	(8)	(9,433,000)
Research on Women's Health.......	(15)	(10,204,000)	(15)	(12,750,000)	(15)	(17,250,000)
Women's Health Initiative........	(16)	(59,121,000)	(16)	(57,000,000)	(16)	(56,819,000)
Minority Health Initiative.......	(2)	(54,813,000)	(2)	(58,297,000)	(2)	(62,797,000)
Loan Repayment Program...........		---		(931,000)		(2,963,000)
Office of Behavioral & Social Sciences Research.............	(3)	---	(3)	(2,240,000)	(3)	(2,363,000)
Total Budget Authority......	700	202,685,000	705	214,465,000	686	230,256,000
Funds reimbursed or directly supporting ICDs...............		(151,586,000)		(159,660,000)		(170,892,000)

Note: Includes FTEs associated with NIH AIDs Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DHHS - National Institutes of Health

Office of the Director
Allocation by Mechanism 1/

(Dollars in thousands)

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
Research Grants:			
Research Projects	$34,266	$41,202	$46,835
Research Centers	---	---	---
Other Research	---	---	---
Total, Res. Grants	$34,266	$41,202	$46,835
Training	29,991	26,642	28,244
R&D Contracts	87,329	91,816	94,813
Intramural Research	1,943	2,837	4,978
Res. Mgmt. and Support	7,155	6,961	7,948
Cancer Control	---	---	---
Construction	---	---	---
Total, ICD	160,684	169,458	182,818
OD Operations	42,001	45,007	47,438
Total	202,685	214,465	230,256

1/ This represents a breakout of the OD's budget as it is ultimately expended by mechanism.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Summary of Changes

1995 Estimated budget authority	$214,465,000
1996 Estimated budget authority	230,256,000
Net Change	+15,791,000

	1995 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Annualization of FY 1995 pay raise		$36,151,000		+$156,000
2. Within grade increase		36,151,000		+592,000
3. One additional day of pay		36,151,000		+151,000
4. FY 1996 Pay Raise		36,151,000		+649,000
5. FECF		36,151,000		+1,000
6. Increased cost of services and supplies		42,650,000		+1,837,000
7. Service and Supply Fund increase		4,606,000		+150,000
8. FTS		226,000		-38,000
Subtotal				+3,498,000
B. Program:				
1. Office of Research on Women's Health	15	$12,750,000		$4,500,000
2. Office of Research on Minority Health	8	8,942,000		+491,000
3. Minority Health Initiative	2	58,297,000		+4,500,000
4. Loan Repayment Program		931,000		+2,032,000
5. Academic Research Enhancement Award Program (AREA)		12,696,000		+1,396,000
6. Office of Alternative Medicine	5	5,398,000		+296,000
7. Office of Behavioral & Social Sciences Research	3	2,240,000		+123,000
8. FTE Reductions	705	36,151,000	-19	-1,045,000
Subtotal			-19	+12,293,000
Total Changes			-19	+15,791,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:	705	686	-19
Full-time equivalent employment.....	705	686	-19
Full-time equivalent of overtime and holiday hours.................	5	5	---
Average ES salary...................	$111,908	$114,146	+$2,238
Average GS/GM grade.................	11	11	11
Average GS/GM salaries..............	$45,142	$46,270	+$1,128
Average salary, grades established by act of July 1, 1944 (42 USC 207)......................	80,066	81,667	+1,601
Personnel Compensation:			
Full-time permanent...............	$28,636,000	$28,255,000	-$381,000
Other than full-time permanent....	1,793,000	1,720,000	-73,000
Other personnel compensation......	594,000	620,000	+26,000
Special personnel service payments......................	162,000	150,000	-12,000
Total, personnel compensation...	31,185,000	30,745,000	-440,000
Personnel benefits..................	4,966,000	4,875,000	-91,000
Travel and transportation of persons..........................	310,000	320,000	+10,000
Transportation of things............	69,000	71,000	+2,000
Rent, communications and utilities..	1,328,000	1,329,000	+1,000
Printing and reproduction...........	614,000	632,000	+18,000

Consultant Services.................	$1,375,000	$3,803,000	+$2,428,000
Other services......................	9,127,000	13,147,000	+4,020,000
Purchasing from government accts....	93,069,000	101,681,000	+8,612,000
Operation of GOCOs..................	---	---	---
R&D contracts.......................	68,591,000	69,711,000	+1,120,000
Supplies and materials..............	750,000	772,000	+22,000
Equipment...........................	3,081,000	3,170,000	+89,000
Total budget authority by object.....	214,465,000	230,256,000	+15,791,000
Funds reimbursed or directly supporting ICDs..................	(159,660,000)	(170,892,000)	(+11,232,000)

Note: These amounts represent funds reimbursed to the ICDs for grant awards.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:	705	686	-19
Full-time equivalent employment.....	705	686	-19
Full-time equivalent of overtime and holiday hours.................	5	5	---
Average ES salary..................	$111,908	$114,146	+$2,238
Average GS/GM grade.................	11	11	11
Average GS/GM salaries..............	$45,142	$46,270	+$1,128
Average salary, grades established by act of July 1, 1944 (42 USC 207)......................	80,066	81,667	+1,601
Personnel Compensation:			
Full-time permanent...............	$28,636,000	$28,255,000	-$381,000
Other than full-time permanent....	1,793,000	1,720,000	-73,000
Other personnel compensation......	594,000	620,000	+26,000
Special personnel service payments.......................	162,000	150,000	-12,000
Total, personnel compensation...	31,185,000	30,745,000	-440,000
Personnel benefits..................	4,966,000	4,875,000	-91,000
Travel and transportation of persons..........................	310,000	320,000	+10,000
Transportation of things............	69,000	71,000	+2,000
Rent, communications and utilities..	1,328,000	1,329,000	+1,000
Printing and reproduction...........	614,000	632,000	+18,000

Consultant Services................	$1,375,000	$3,803,000	+$2,428,000
Other services.....................	9,127,000	13,147,000	+4,020,000
Purchasing from government accts....	2,000,000	1,500,000	-500,000
Operation of GOCOs.................	---	---	---
R&D contracts......................	91,816,000	94,813,000	+2,997,000
Supplies and materials.............	750,000	772,000	+22,000
Equipment..........................	3,081,000	3,170,000	+89,000
Grants, subsides and contributions 1/	67,844,000	75,079,000	+7,235,000
Total budget authority by object.....	$214,465,000	$230,256,000	+$15,791,000
Funds reimbursed or directly supporting ICDs..................	(159,660,000)	(170,892,000)	(+11,232,000)

Note: This represents breakout of the OD's budget by object class requesting how funds are ultimately expended.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)........	$28,636,000	$28,255,000	-$381,000
Other than full-time perm. (11.3).	1,793,000	1,720,000	-73,000
Other personnel compen. (11.5)....	594,000	620,000	+26,000
Special personnel service payments (11.8)................	162,000	150,000	-12,000
Total Personnel Comp. (11.9)........	31,185,000	30,745,000	-440,000
Civilian Personnel Benefits (12.1)..	4,966,000	4,875,000	-91,000
Benefits to Former Personnel (13.0).	---	---	---
Travel (21.0)......................	310,000	320,000	+10,000
Transportation of Things (22.0).....	69,000	71,000	+2,000
Rental Payments to Others (23.2)....	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3)......	1,328,000	1,329,000	+1,000
Printing and Reproduction (24.0)....	614,000	632,000	+18,000
Consulting Services (25.1)..........	1,375,000	3,803,000	+2,428,000
Other Services (25.2)...............	9,127,000	13,147,000	+4,020,000
Purchase of Goods & Services from other Government Accounts (25.3)...	93,069,000	101,681,000	+8,612,000
Operation of GOCOs (25.4)...........	---	---	---
Supplies and Materials (26.0).......	750,000	772,000	+22,000
Total............................	142,793,000	157,375,000	+14,582,000

Note: The increase in Other Services (25.2) reflects the growth in the Non-Aids Loan Repayment Program.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)........	$28,636,000	$28,255,000	-$381,000
Other than full-time perm. (11.3).	1,793,000	1,720,000	-73,000
Other personnel compen. (11.5)....	594,000	620,000	+26,000
Special personnel service payments (11.8)................	162,000	150,000	-12,000
Total Personnel Compensation (11.9).	31,185,000	30,745,000	-440,000
Civilian Personnel Benefits (12.1)..	4,966,000	4,875,000	-91,000
Benefits to Former Personnel (13.0).	---	---	---
Travel (21.0)......................	310,000	320,000	+10,000
Transportation of Things (22.0).....	69,000	71,000	+2,000
Rental Payments to Others (23.2)....	---	---	---
Communications, Utilities, and Miscellaneous Charges (23.3)......	1,328,000	1,329,000	+1,000
Printing and Reproduction (24.0)....	614,000	632,000	+18,000
Consulting Services (25.1)..........	1,375,000	3,803,000	+2,428,000
Other Services (25.2)...............	9,127,000	13,147,000	+4,020,000
Purchase of Goods & Services from other Government Accounts (25.3)...	2,000,000	1,500,000	-500,000
Operation of GOCOs (25.4)...........	---	---	---
Supplies and Materials (26.0).......	750,000	772,000	+22,000
Total..........................	51,724,000	57,194,000	+5,470,000

Note: The increase in Other Services (25.2) reflects the growth in the Non-Aids Loan Repayment Program.

Note: This represents breakout of the OD's budget by administration expenses requesting how funds are ultimately expended.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

SIGNIFICANT ITEMS IN HOUSE AND SENATE
APPROPRIATIONS COMMITTEE REPORTS

Item	
1995 House Report	
Women's Health Initiative	
1. The House in its report 103-553, page 66, stated, "The Committee continues to support the Women's Health Initiative and encourages NIH to modify the study as recommended by the Institute of Medicine to the extent that it deems appropriate."	1. The Institute of Medicine (IOM) recommended four modifications to the study. 1) The first recommendation that the informed consent needs modifications. The Women's Health Initiative (WHI) responded by modifying existing forms to include quantitative estimates of risk and benefit particularly in the hormone replacement therapy arms of the Clinical trial, sought the approval of the Data and Safety Monitoring Board, sought approval of the investigators and are currently attempting to balance the concern for the participants by making it more understandable for all levels of education. 2) The second recommendation was to shift emphases from testing the link between dietary modification and breast cancer to testing the link between dietary modification and coronary heart disease. The primary question addressed in the dietary modification study is whether a low-fat dietary pattern prevents development of breast cancer. This dietary pattern also has potential benefits for prevention of colorectal cancer and coronary heart disease. The evidence indicating a link between diet and breast cancer in postmenopausal women is conflicting and inconclusive, but the issue has extraordinary public health importance. In this situation a properly designed randomized clinical trial is the

only means of establishing convincing proof of causality and justification for public health prevention programs. The hypothesis linking diet and colon cancer is suggestive but also not proven. The hypothesis linking dietary pattern to both cancers merits testing and has great public health relevance. On the other hand, the evidence linking diet to coronary heart disease is quite firm and has led to important decreases in coronary heart disease mortality in women and men. While the proposed WHI dietary intervention should beneficially affect coronary heart disease, there is no imperative to test this generally accepted relationship in a large clinical trial with this as the primary endpoint. 3) The third recommendation was that the clinical trial component of the initiative should be scheduled to end after six years as opposed to nine years as designed by NIH. The discussion clarified the recommendation of the IOM regarding Objective Prescheduled Reassessment and there is agreement that as part of the monitoring of the clinical trial, a comprehensive assessment of the clinical trial at an average follow-up of 6 years will be undertaken. This assessment will lead to a recommendation to the Director of NIH on whether or not to continue, and if needed, with what modifications. The fourth recommendation was that the cost of the clinical trial alone will be more expensive than estimated by WHI and will exceed the $625 million. The WHI agrees that the budget is tight and that careful monitoring is needed. It is imperative, however, that the quality of the studies and its components be maintained at a high level within the budget. The investigators, through a streamlining task force, are currently evaluating methods for maximizing the use of available funds.

Office of Research on Minority Health

2. The House in its report 103-553, page 67, stated, "The ORMH and NIDDK are working jointly to promote the health of minority populations through research on the genetics of diabetes and on diabetes treatment and prevention in minority populations. The Committee is pleased with this cooperation and urges ORMH to continue its efforts through the Minority Health Initiative to support a broad range of research grants on the fundamental causes of diabetes in minority populations, with emphasis on the genetics of diabetes and its associated risk factors, such as obesity."

2. The ORMH and the NIDDK are closely cooperating in a number of ongoing joint initiatives. The ORMH is providing support for a major new NIDDK-funded clinical trial for the prevention of Non-Insulin-Dependent Diabetes Mellitus (NIDDM). This trial, which will include over 50% minority participants, will test preventive interventions in individuals at risk of developing NIDDM, including minority women with a history of gestational diabetes. The NIDDK and the ORMH also are co-funding research on the pathogenesis of diabetes in Mexican-American women. NIDDK is continuing to support grants focussing on genetics of diabetes in minorities that were initiated through ORMH start-up funding. In addition, ORMH is contributing to small clinical studies of diabetes in urban Native American youth, Pueblos, Zuni youth, and Hispanics. These studies resulted from two NIDDK solicitations targeting minority research.

Indirect Costs

3. The House in its report 103-553, page 67, stated, "The Committee has not included bill language proposed by the Administration that would create a one-year "pause" in indirect cost payment increases to institutions receiving research support from NIH. The Committee does not feel that the Administration's proposal addresses key underlying problems, such as a disparity in indirect cost rates among institutions. The Committee is very concerned, however, about the share of research dollars that is consumed by indirect costs. With the current budgetary ceilings, funding for all research is tightly constrained, and every dollar allocated for indirect costs reduces

3. As part of its comprehensive review of indirect costs reimbursement policies, the NIH participated in the development of the Administration's proposed reform of indirect costs through the National Science and Technology Council. These proposals will help reduce the range of rates, standardize the costs, and streamline the process. Additionally the Administration is proposing to phase out the allowability of tuition as a benefit under Office of Management and Budget Circular A-21, Cost Principles for Educational Institutions. This change is consistent with the Federal Acquisition Regulation and a

the funding available for the direct costs of basic and clinical research. The Committee believes a revision to indirect cost allocation is urgently needed. The Administration has indicated that the Office of Management and Budget intends to work with affected institutions to study the issue. While acknowledging that indirect costs are complex, the Committee notes that the issue has been studied exhaustively and believes the time has come to implement concrete proposals. The Committee intends to serve notice that, if the Administration has not developed revisions to the indirect costs allocation process by the time the 1995 appropriations bill goes to conference, it may address the problem legislatively.

forthcoming recommendation of the General Accounting Office.

Outcomes for Research Grant Applicants

4. The House in its report 103-553, page 69, stated, "Throughout the 1995 hearings, the Committee raised questions about what is known about the career paths and funding sources for those researchers who are unsuccessful in applying for NIH grants. In a preliminary attempt to answer this question, NIH reviewed the fiscal year 1990 cohort of applicants for research project grants to see how many ultimately received NIH research funding. The study found that, by the end of 1993, 39 percent of the applicants remained unfunded by NIH. However, only 10 percent of those whose applications scored in the top fifty percent remained unfunded. The Committee found these results very interesting and worthy of further analysis and directs NIH to conduct a more thorough, longer-term study of this question. Such an analysis should include, to the extent possible, the participation of the unfunded researchers in other NIH grants, such as centers or research

4. In response to fiscal year 1995 report language from the House Subcommittee on Labor, Health and Human Services, Education and Related Agencies, the NIH has used data in existing databases to examine the subsequent research funding experiences of unsuccessful NIH research grant applicants. This type of analysis showed that 71% of the original applicants for funding in fiscal year 1990 received some type of independent research support from the NIH by the end of fiscal year 1993. It is very likely that some portion of the remaining 29% of the applicants received support from staff positions on NIH research grants and from other Federal and non-Federal sources. We are in the process of designing a survey to track a cohort of the unfunded applicants forward in time. This survey will provide information on the retention of scientists in research careers, how they are funded, and how Federal support acts in tandem with other sources of

project grants, for which they are not the principal investigator. In addition, the question of funding from non-NIH sources, such as the National Science Foundation, private industry, and foundations, should be pursued. Understanding that a properly conducted survey will require a significant amount of time, the Committee does not set a precise timetable for completion, but urges NIH to begin work promptly so that some findings may be available in time for the 1996 appropriations hearings."	support. We expect to complete the design, seek OMB approval for the survey, and initiate data collection during the current fiscal year.
Staffing Ceilings	
5. The House in its report 103-553, page 70, stated, "The Committee recognizes the difficulties NIH faces in adequately staffing research areas, due to the government-wide effort to downsize personnel. The Committee urges NIH to use its internal waiver authority within its overall staff ceiling to permit proper staffing of the highest priority research areas."	5. The NIH will continue to effectively staff high priority research activities as part of its management of its overall FTE ceiling and in support of its intramural research streamlining goals to provide for resource sharing and to maintain a rigorous review of scientific programs to assure efficient use of resources.
1995 Senate Report	
Health of Alaska Natives	
1. The Senate in its report 103-318, pages 111-112, stated, "The Committee is concerned about statistics brought to its attention which show dramatically poor health status indicators for the Alaska Native population. Specific health problems which have been identified include infectious and chronic health problems, various cancers, and behavioral problems such as fetal alcohol syndrome, suicide, and unintended injury and death. The Committee urges the Director of the National Institutes of Health to make a review of the state of research in this area and to be prepared to report to the subcommittee during its fiscal year 1996 hearings on strategies to	1. The NIH is aware of the health challenges facing the indigenous peoples of Alaska and the Arctic. It is clear that strategies to improve the health of this population must deal with linguistic and cultural barriers to traditional programs as well as geographic, socioeconomic, and underserved population problems. However, progress is being made toward addressing the chronic health problems of Alaska Natives, and strategies for future interventions have been developed. Efforts are currently underway that relate specifically to such health problems as cancer, diabetes, infectious diseases, communication disorders and mental health, among others.

address these health problems of indigenous peoples of Alaska and the Arctic, as well as the biomedical basis for understanding these so far largely unaddressed problems."

Additional efforts are focused on encouraging Alaska Natives to pursue biomedical careers and develop skills in research methodology. The approach used by the NIH in this endeavor can be characterized as locally interactive. Several meetings were held in the state of Alaska in FY 1994. In addition, the full range of mechanisms available to NIH is being used to forge partnerships with Alaska Natives, including planning grants, travel grants and conference/workshop grants. In this way NIH has collaborated with Federal government agencies, such as the Indian Health Service; state government agencies, such as the Alaska Department of Health and Social Services; and community-based organizations, such as the Alaska Native Medical Center, to reach its goals. Information dissemination is a critical factor in combating these problems. Major efforts are being made to avail Alaska Natives of the latest and most current information that relates to their specific health problems. Through efforts of the National Library of Medicine to establish internet hook-ups and through the production of new publications, such as the monograph, "Cancer Risk Factors Among Alaska Natives" and "Cancer Education Resources for American Indian and Alaska Natives," this population is becoming connected to the resources that NIH has to offer.

Women, Minorities, and Social Work Research

2. The Senate in its report 103-318, page 113, stated, "The report by the NTM social work research task force identified a serious lack of NIH support for doctoral and postdoctoral research training and research career development in social work. The Committee encourages the Director to consider establishing a task force to explore

2. In FY 1995, NIMH funded the second Social Work Research Development Center at the School of Social Work at the University of Tennessee. Three Research Enhancement Projects which include Partners Network Project, Oregon Partners Project Evaluation and Preventing Mental Health Problems in Multirisk Infants were funded this

with the social work research community ways to advance social work research development throughout NIH.	year. Also R24s will be funded this year. NIMH is interested in supporting the development of research careers for social workers. The Institute encourages young investigators to explore the area of social work, including minority doctoral candidates through pre- and postdoctoral fellowships, training grants, and research dissertation support. In FY 1994, NIMH supported 15 social work predoctoral candidates. There were no applications for postdoctoral fellowships. Social workers are also eligible for Research Career awards (R mechanism), a number of which offer support for additional research experience or to modify current career paths. The Director will consider the recommendations of the Committee concerning a task force to explore social work research.
Additionally, the Committee remains concerned about the lack of women and minorities in clinical trials, funded research, and leadership positions at NIH."	In accordance with the NIH Revitalization Act of 1993, it is NIH policy that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human research subjects, including clinical trials, unless a clear and compelling rationale and justification supports the determination that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The inclusion of women and members of minority groups and their subpopulations must be addressed in each application submitted for funding. Such proposals must include a research design which incorporates an outreach plan for recruiting women and minorities. NIH funding components will not award any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 or thereafter which does not comply

with this policy. The ORWH has focused on the development of expanded opportunities and support for increased recruitment, retention, re-entry, and advancement of women in biomedical careers, including those women scientists at the NIH. The ORWH is also collaborating with other NIH offices, such as the Office of Equal Opportunity, and with groups, such as the NIH Intramural Women Scientists Advisory Committee, to support efforts to improve the status of women scientists at the NIH.

Neuroscience Research

3. The Senate in its report 103-318, page 113, stated, "The Committee is very encouraged by the progress that has been made since the implementation of the "Decade of the Brain" in 1990, and urges the NIH to make this one of its highest research priorities at the nine individual institutes that conduct neuroscience research. The Committee requests that the Director of the NIH report at next year's Committee hearings on the progress of this effort."

3. The NIH recognizes that neuroscientists have identified major areas of extraordinary promise in understanding how the brain develops and regulates the body. In FY 1994, in addition to the overall efforts of the nine of the NIH institutes that support projects in the "Decade of the Brain," the NIH Director asked the Institutes to nominate neuroscience projects of high quality that could not be supported under regular funding circumstances. Using discretionary funds, the Director transferred an additional $2.4 million to nine Institutes to facilitate neuroscience research and to maximize the benefits of that research. Further progress in this effort will be reported at the Committee hearings.

Indirect Costs

4. The Senate in its report 103-318, page 115, stated, "The Office of Science and Technology Policy (OSTP), in consultation with the research community, has begun a comprehensive review of indirect costs, as called for in the administration's budget proposal. The Committee expects that this

4. As part of its comprehensive review of indirect costs policies, the NIH participated in the development of the administration's proposed reform of indirect costs through the National Science and Technology Council. These proposals will help reduce the range of rates, standardize the costs, and

process be considered carefully, and geared to arrive at a timely and long-term solution to the indirect cost issue. Additionally, the Committee has received reports that many universities that receive NIH grants are permitted to charge to grants the cost of tuition for faculty, staff, and their families. It is the Committee's understanding that these benefits are not covered by regulations that apply to defense contractors and other Government suppliers. The Committee believes that this matter should be addressed by the administration's comprehensive review."

streamline the process. Additionally the administration is proposing to phase out the allowability of dependent tuition as a benefit charged directly and indirectly to federally-sponsored research under Office of Management and Budget (OMB) Circular A-21, Cost Principles for Educational Institutions. This change is consistent with the Federal Acquisition Regulation and a forthcoming recommendation of the General Accounting Office. OMB will publish this proposed change in the Federal Register concurrent with transmittal of the President's FY 1996 Budget.

Diagnostic Radiology

5. The Senate in its report 103-318, page 116, stated, "The Committee believes that every opportunity to improve diagnostic techniques must be aggressively pursued. The Committee, therefore, encourages NIH to explore ways in which the diagnostic radiology programs now spread throughout the various research institutes could be better coordinated."

5. The NIH Deputy Director for Intramural Research has organized an "Imaging Task Force" to explore the organizational and resource limitations to radiological and other medical imaging research on the NIH campus. Members of this task force, consisting of the leadership of all of the major imaging facilities on the NIH campus, will be joined by several outside consultants to evaluate current coordination and resource management of imaging facilities at the NIH. One of these NIH facilities is the Laboratory for Diagnostic Radiology Research (LDRR) which does state-of-the art research on novel radiological imaging technologies, such as MRI, and trains radiology fellows in these new techniques. The Task Force will explore ways to improve the effectiveness of LDRR and other diagnostic radiology programs at the NIH through enhanced coordination of research and training activities and improved resources.

Academic Research Enhancement Award

6. The Senate in its report 103-318, page 116, stated, "The Committee urges NIH to consider the overall level of NIH support for an academic institution, rather than only the level of support provided to a school within an institution when awarding grants."

6. The AREA program is designed to stimulate research in educational institutions that provide baccalaureate training for a significant number of the Nation's research scientists, but historically have not been major recipients of NIH support. Competition for AREA grants are open to those institutions or organizational components thereof. The schools within a university that do not receive significant support from the NIH are considered to be AREA-eligible also in order to create or enhance a research opportunity for scientists and students in those university components that are unlikely otherwise to participate extensively in the NIH's biomedical and behavioral research effort. For example, rather than considering the University of South Carolina at Columbia as a single entity for determining eligibility under the AREA program, this policy allows its School of Pharmacy, School of Public Health, and School of Nursing to compete for AREA awards as if each was a separate institution, per se. This holds true, say, for the School of Verterinary Medicine, University of Illinios at Urbana-Champaign; it also is eligible to apply for AREA grants because it is treated as if it were a single entity in and of itself. Further, we have heard of instances where a university's School of Pharmancy or its School of Biologicial Sciences are part of the same campus as the School of Medicine, but because there is no or little interaction between the two, that smaller component(s) receives no benefit from its proximity to the School of Medicine; and, in fact, that is the case in a number of schools. Therefore, we believe that this policy increases cross-school collaboration and intra-research

	support among university components and its students that would not exist otherwise.
Impact of Alcohol on Cardiovascular Health	
7. The Senate in its report 103-318, page 117, stated, "There is also evidence from epidemiologic studies suggesting that moderate alcohol consumption may be positively associated with cardiovascular health. In addition to alcohol, wine contains antioxidants that may offer a protective element for cardiovascular disease. The Committee urges the National Institutes of Health to support and assist research efforts in these areas, especially the impact of alcohol on cardiovascular health and longevity and on the dietary role of antioxidants and moderate alcohol consumption, and to develop a working strategy to assure future research on this important issue."	7. Epidemiologic studies have consistently shown that moderate alcohol use is associated with a reduced risk of coronary heart disease and ischemic stroke. Protective mechanisms appear to include favorable effects on blood lipids and clotting factors, and may include others, such as increased estrogen and decreased insulin levels. The NHLBI and NIAAA recognize that more research is needed to better understand these mechanisms, and to understand the role of non-alcohol factors such as antioxidants. The NIH will continue to support an active research program in this area.
Technology Transfer	
8. The Senate in its report 103-318, page 114, stated, "The Committee is dismayed that, to date, technology transfer efforts at the NIH have been unable to effectively address important policy and legal issues necessary to support the execution of cooperative research and development agreements [CRADA]. Specifically, the Committee is concerned about NIH technology transfer capabilities with regard to carrying out the necessary fiduciary and legal responsibilities related to patent prosecution; staff capabilities with respect to representing NIH interests in commercialization of research, negotiating commercial issues related to collaborations with industry, and working as full partners in the CRADA process with industry; and internal communication	8. Generally, the NIH shares the Committee's concerns with improving the effectiveness of the technology transfer program and has taken a number of steps to address these issues. NIH has recently selected a new permanent Director for the Office of Technology Transfer (OTT) and has made major changes in the OTT organizational structure and in its reporting relationship within the Office of the Director, NIH. In addition, in the last several months a new Public Health Service Technology Policy Board, chaired by the Acting Director for Science Policy and Technology Transfer, NIH, has been established to set overall PHS technology transfer policy. To help implement the Board's guidance and to improve the functioning of the NIH technology transfer program, a NIH Technology Transfer Advisory

and coordination with regard to execution of CRADA's within the categorical institutes and the NIH overall. The Committee believes that these issues serve as the greatest deterrents to industry's willingness to collaborate with the NIH and participate in technology transfer. These factors have raised serious concerns with the Committee about the NIH's ability to carry out its mandate of technology transfer. The Committee will continue discussions with the Director, NIH on these important matters and is anxious to see NIH develop a plan with expediency to address these concerns."	Committee (TTAC) has been formed. A standing subcommittee of the TTAC will focus on CRADAs. Moreover, the recent "External Advisors Report on the NIH Intramural Program" shared many of the same concerns expressed by Congress and made several specific recommendations that NIH is committed to implement in order to improve its technology transfer efforts. The NIH looks forward to continuing to work with Congress to ensure that the American public can benefit from the fruits of the taxpayer investment in biomedical research.
Intramural Research	
9. The Senate in its report 103-318, page 114, stated, "The Committee encourages the Director to implement...suggested reforms, and requests the NIH to plan a plan for the renovation of a downsized research hospital to replace the existing clinical center. That plan should also include a proposal for financing the cost of this facility, to the maximum extent possible, by reallocating existing resources. In addition, the Committee shares the advisory committee's concerns about the impact of the Federal Government's overall personnel downsizing proposal on the level of bench scientists in the NIH's Intramural Research Programs."	9. In accordance with the administration's streamlining goals, NIH's streamlining plans call for reductions of little less than 1,500 FTEs (-9%) over the 5 year period between FY 1995 & FY 1999. Although every effort will be made to minimize reductions to our scientific capabilities, the overall size of the reduction in employment envisioned for NIH and the large proportion of existing employees who are research scientists, or who supports the Intramural Research Program (IRP) dictates a smaller program. The leadership of the NIH and the Scientific Directors of the IRPs will reduce the impact of this downsizing on the scientific program by continued exercise of rigorous oversight of the quality of research and research personnel in the IRPs. The following mechanisms have evolved to assure this quality control: a tenure-track system which allows scientists newly recruited as a result of national searches a period of 6 years of independent research support with yearly evaluations and two reviews and an external advisory board prior to making a decision about a permanent position; highly selective rigorous

	tenure system for independent scientists including review by an external Board of Scientific Counselors, review by an ICD-based promotion and tenure committee, a recommendation by the Scientific Director based on these reviews and a recommendation by a Central Tenure Committee to the Deputy Director for Intramural Research who makes the final tenure decision; and every 4 years every research laboratory at the NIH is rigorously reviewed by external Boards of Scientific Counselors which make explicit recommendations to the Scientific Directors of each ICD with an IRP, concerning the resources of each tenured and tenure-track scientist, including overall budget, space and personnel allotments. This system assures that limited resources will be wisely distributed. Over the next few years, the Clinical Center hospital will be reduced from its current 450 beds to a 250 bed hospital to fit into the envelope of the new dormsized hospital building.

1995 Conference Report

Transfer Authority

1. The Conference in its report 103-733, page 18, stated, "The conference agreement provides authority for the Director to transfer up to one percent of the National Institutes of Health (NIH) appropriation to activities he may designate. The conferees reiterate that such transfers are subject to normal reprogramming procedures and not merely a notification to Congress of actions taken."	1. The Director, NIH has the authority to transfer up to one percent of the NIH appropriation provided that no ICD appropriation is increased or decreased by more than 1% by any such transfer, and that Congress is promptly notified of the transfer. This gives the Director the flexibility to apply funds to meet significant research opportunities and high priority initiatives. These transfers are subject to normal reprogramming procedures. The NIH is currently forwarding a document through established DHHS channels proposing transfers for FY 1995.

Indirect Costs Payments to Institutions

2. The Conference in its report 103-733, page 10, stated," The conferees reiterate the concerns expressed in both the House and Senate reports relating to indirect cost payments to institutions receiving NIH research funding. The conferees continue to believe that this is an area in need of review and are encouraged that the Administration has committed to a comprehensive review and revision of indirect cost procedures. The conferees expect to see the Administration's proposals for dealing with indirect costs, and particularly the disparities between institutional rates, in the context of the fiscal year 1996 budget submission."

2. Following transmittal of the President's FY 1996 Budget, the Administration launched an interagency effort to examine current indirect cost policies and to develop proposals to improve the present process through the National Science and Technology Council. NIH participated directly through the Committee on Fundamental Science, which formulated proposals to stabilize the Federal reimbursement of indirect costs; narrow the range of indirect costs rates; and develop simplified methodologies for financing research facilities. The Administration plans address these changes in the President's FY 1996 in the Federal Register Budget and to concurrently publish proposed changes in OMB Circular A-21.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Funded Authorizations:						
Office of the Director..............	Title IV, Section 402(b)	40 USC282	Indefinite	$214,465,000	Indefinite	$230,256,000
Total Budget Authority...				$214,465,000		$230,256,000
Funds reimbursed or directly supporting ICDs..................				($159,660,000)		($170,892,000)

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$36,701,000	$246,651,000	$56,708,000	$57,463,000 2/3/
1988	59,819,000	71,389,000 4/	61,284,000	61,819,000
1989	59,578,000	71,578,000	65,578,000	72,201,000
1990	96,570,000	106,987,000	127,570,000	108,468,000 5/
1990 Sequester				-1,049,000
1991	82,975,000	106,175,000	77,975,000	97,651,000 6/
1991 Sequester				-1,000
1992	95,176,000	149,176,000	125,724,000	142,112,000 7/
1993	203,430,000	194,275,000	188,400,000	190,325,000 8/
1994	234,907,000	224,746,000	241,225,000	227,190,000 9/
1995	233,522,000	244,745,000	240,316,000	217,929,000 10/11/
1996	230,256,000 10/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Includes a transfer of $755,000 to cover the FERS increase and partial costs of the pay raise.

3/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes.

4/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

5/ Excludes enacted administrative reduction of $519,000.

6/ Excludes enacted administrative reductions of $2,924,000.

7/ Excludes enacted administrative reductions of $1,459,000, and enacted rescission of $258,000.

8/ Excludes enacted administrative reductions of $2,438,000.

9/ Excludes an enacted administrative reduction of -$6,415,000.

10/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

11/ Excludes enacted administrative reductions of $438,000.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Activity
(Dollars in thousands)

	1992 1/ Actual		1993 1/ Actual		1994 1/ Actual		1995 1/ Appropriation		1996 1/ Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research Management and Support.............	699	$129,853	716	$175,311	700	$202,685	705	$214,465	686	$230,256	-19	+$15,791
Unobligated balance start of year.................	---	-1,504	---	---	---	---	---	---	---	---	---	---
Unobligated balance end of year.................	---	1,867	---	---	---	---	---	---	---	---	---	---
Subtotal obligations.......	---	130,216	---	175,311	---	202,685	---	214,465	---	230,256	---	+15,791
Unobligated balance lapsing.................	---	249	---	70	---	---	---	---	---	---	---	---
Total budget authority...	699	130,465	716	175,381	700	202,685	705	214,465	686	230,256	-19	+15,791
Funds reimbursed or directly supporting ICDs..........		(85,952)		(127,808)		(151,586)		(159,660)		(170,892)		(+11,232)

1/ The FY 1992 actual, FY 1993 actual, FY 1994 actual, the FY 1995 appropriation, and the FY 1996 estimate excludes $1,128,000, $9,277,000, $7,334,000 and $5,000,000 and $5,000,000 respectively, in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

Office of the Director

FY 1994 Authority		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
700	$202,685,000	705	$214,465,000	686	$230,256,000	-19	+$15,791,000
	(151,586,000)*		(159,660,000)*		(170,892,000)*		(+11,232,000)*

*Funds Reimbursed or Directly Supporting ICDs.

General Statement

This document provides justification for the FY 1996 non-AIDS activities of the Office of the Director (OD), National Institutes of Health (NIH). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The appropriation for the OD of the NIH provides funds for the central administration of, and services to, the NIH Institutes, Centers and Divisions (ICDs). While each major research component of the NIH administers the activities associated with its specific programs, the Office of the Director is responsible for their overall direction and coordination. The major units within the OD are responsible for central functions such as extramural and intramural research policy; and the coordination of technology transfer and scientific policy; coordination and direction of research on the health of women and minorities as well as research training programs for these populations; legislation, program planning and evaluation; coordination of public affairs and communication activities; contract and grant administration; and financial and personnel management. A number of other offices are responsible for promotion of disease prevention, medical applications of research, and for NIH-wide direction and centralized services in such areas as equal opportunity, procurement, and information resources management.

During the last five years there has been substantial growth in the OD appropriation. However, approximately 72 percent of this growth has been in programs of a cross-cutting nature such as the Women's Health Initiative, the Minority Health Initiative, and the Science Education and the Alternative Medicine Programs. While funds are initially budgeted in the OD, and the OD provides the overall direction, coordination and oversight, actual program operations are conducted within the ICDs. For example in FY 1996 $170,892,000 of the FY 1996 budget request of $230,256,000 is anticipated to be reimbursed to ICDs for their direct support of the specific programs.

150

The President's appropriation request of $230,256,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the OD during the last five years has been as follows:

	Amount	Funds Reimbursed or Directly Supporting ICDs	FTEs
FY 1991	$84,407,000	($47,438,000)	666
FY 1992	130,465,000	(85,952,000)	699
FY 1993	175,381,000	(127,808,000)	716
FY 1994	202,685,000	(151,586,000)	700
FY 1995	214,465,000	(159,660,000)	705

Purpose and Method of Operation

The Office of the Director provides leadership and direction to the NIH research community, and coordinates and directs initiatives which cut across the NIH. The OD is responsible for the development and management of intramural and extramural research and research training policy, the review of program quality and effectiveness, the coordination of selected NIH-wide program activities, and the administration of centralized support activities essential to the operation of the NIH.

Several offices in the OD provide policy and direction to the NIH research community:

The Office of Extramural Research (OER) advises the NIH Director and provides guidance to NIH Institutes, Centers and Divisions (ICDs) on matters relating to the management of extramural research. The Office reviews, regulations, policies, and procedures, and trains staff to promote effective stewardship of extramural research and training programs; peer review of extramural awards and administration of grants. The Office also monitors certain conditions placed on extramural awards, including the protection of human subjects, the welfare of animals, the inclusion of women and minorities in study populations, and the responsible conduct of research to ensure that NIH awardee institutions meet or exceed Federal requirements.

The primary function of the Office of Intramural Research (OIR) is to oversee the conduct of biomedical research within NIH's laboratories and clinics, ensuring and maintaining an environment that fosters the highest possible quality of research. Specific aspects of this endeavor include: oversight and formulation of policy for the recruitment and retention of an outstanding and diverse scientific staff; development of new programs to enrich communication and the exchange of new knowledge among scientists; promulgation of policies and measures to enhance the appropriate conduct and evaluation of research; protection of human subjects and laboratory animals; oversight of laboratories for diagnostic radiology research and the production of purified proteins for AIDS and other pharmacological and basic research; and the administration of an educational program for NIH scientists.

The Office of Disease Prevention (ODP) provides leadership, coordination, and support to biomedical programs that seek to improve the nation's health through research and application of preventive strategies. This office is also responsible for coordinating the Disease Prevention and Health Promotion research programs of the component ICDs of the NIH and collaborates with other Administration agencies and the private sector to maximize prevention programs. This office is also responsible for conducting the Women's Health Initiative and for development of Consensus Development Conferences.

The Office of Research on Women's Health (ORWH) works in collaboration with the ICDs of the NIH to promote and foster efforts to address gaps in knowledge related to women's health through the enhancement and expansion of funded research and/or the initiation of new investigative studies. The ORWH is responsible for ensuring the inclusion of women in clinical research funded by the ICDs, including the development of a computerized tracking system and the implementation of new guidelines on such inclusion as mandated in the 1993 NIH Revitalization Act. This Office is also involved in promoting programs to increase the number of women in biomedical scientists, and in the development of women's health as a focus of medical/scientific research. The ORWH responds to public, scientific and advocacy communities in its collaborative efforts throughout the NIH to promote research on women's health.

The Office of Research on Minority Health (ORMH) serves as the coordinating office for minority health research and research training activities at the NIH. Through partnerships with the ICDs, other federal agencies and outside organizations, the ORMH strives to improve the health status of all minorities and increase the numbers of minority scientists. An integral part of the ORMH's responsibilities is the implementation and assessment of the Minority Health Initiative, a coordinated set of programs designed to address the health needs of minorities across the lifespan and to expand the participation of minorities in all phases of biomedical and biobehavioral research. Additional activities of the ORMH include providing supplemental support to ICD projects, developing programs to increase minority participation in clinical trials, initiating and supporting infrastructure development projects at minority institutions, and developing programs to increase the competitiveness of grant applications submitted by minority researchers.

The Office of Science Policy and Technology Transfer (OSPTT) provides leadership, direction and coordination regarding all phases of technology transfer and science policy. OSPTT addresses issues in areas where science interfaces with society at large. These include a broad array of ethical, legal, social and economic issues that emerge from biomedical and behavioral research. OSPTT also manages technology transfer activities, providing advice and assistance as well as direct services to all Administration agencies. Planning and program evaluation constitutes a significant component of OSPTT, as well as do the activities associated with the NIH Recombinant DNA Advisory Committee.

There are also a number of administrative and managerial support functions in the Office of the Director:

The Office of Communications (OC) seeks to improve understanding of NIH programs, activities, and research accomplishments on the part of the general public, Congress, biomedical institutions and the medical profession. The OC also has the responsibility for coordinating the public affairs and information dissemination activities of the ICDs.

The Office of Equal Opportunity (OEO) advises the Director, NIH, and staff on matters related to diversity, civil rights, Equal Employment Opportunity (EEO) programs and policies. The OEO maintains liaison with NIH components that administer programs to increase the participation of minorities in biomedical research; provides for investigation of discrimination complaints; and ensures affirmative hiring and promotion practices, and maintains compliance with laws, rules and regulations governing contracts and grants.

A number of other offices are responsible for providing leadership and guidance in all phases of management; and advises the NIH Director and his staff in the areas of information resources management, budget and financial management, personnel management, management assessment and internal control, grant and contract management, procurement, logistics, engineering services, safety, space and facility management, and security operations.

Overall Budget Policy

The FY 1996 budget request for the Office of the Director is $230,256,000. This represents an increase of $15,791,000 over the comparable FY 1995 level of $214,465,000. Essentially all of the increase (71 percent, $11,232,000) is to reimburse ICDs for the programs or research contracts in support of trans-NIH programs (e.g. Minority Health Initiative and Women's Health Initiative).

The request includes $56,819,000 for the Women's Health Initiative; $17,250,000 for the Office of Research on Women's Health; $62,797,000 for the Minority Health Initiative; and $9,433,000 for the Office of Research on Minority Health. Other highlights include $7,499,000 for the Director's Discretionary Fund, $14,092,000 for the Academic Research Enhancement Award (AREA) Program, $2,015,000 for the Diagnostic Radiology Research Program, $5,694,000 for Office of Alternative Medicine, $1,893,000 for Science Education, $2,963,000 for the Loan Repayment Program, $2,363,000 for the Office of Behavioral & Social Sciences Research and $47,438,000 for the central OD program offices. The request includes 686 FTEs, as compared to the FY 1995 level of 705.

Research Management and Support

Authorizing legislation - section 402(b) of the Public Health Service Act.
1996 authorization: Indefinite

FY 1994 Authority		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
700	$202,685,000	705	$214,465,000	686	$230,256,000	-19	+$15,791,000
	(151,586,000)*		(159,660,000)*		(170,892,000)*		(+11,232,000)*

*Funds Reimbursed or Directly Supporting ICDs.

The Office of the Director (OD) supports research and research training in the biomedical sciences through the formulation and coordination of NIH policy. The President's appropriation request of $230,256,000 for this account represents current law requirements. No amounts related to proposed legislation are included. Funding for the OD during the last five years has been as follows:

	Amount	Funds Reimbursed or Directly Supporting ICDs	FTEs
FY 1991	$84,407,000	($47,438,000)	666
FY 1992	130,465,000	(85,952,000)	699
FY 1993	175,381,000	(127,808,000)	716
FY 1994	202,685,000	(151,586,000)	700
FY 1995	214,465,000	(159,660,000)	705

Women's Health Initiative

The Women's Health Initiative (WHI) is a clinical trial to test promising preventive interventions for cancer, heart disease, and osteoporosis; an observational study to define new predictors and biomarkers for disease and risk status; and a community prevention study to test approaches to improving healthful behaviors, particularly for minority women. This is a 15 year project with the first year devoted to research design and the second and third years to contract awards. The WHI is under the auspice of the Office of Disease Prevention.

Contracts for 24 more clinical centers were awarded in FY 1994 for a total of 40. The contracts for the original 16 Vanguard Clinical Centers were awarded in FY 1993. The new centers are scheduled to begin recruitment in February 1995. Having selected all the 40 clinics in FY 1994, major aspects of recruitment of the 63,000 women in the clinical trial and the 100,000 women in the observational study will be underway in February of 1995. The enrollment at seven of the new centers will specifically include 60 percent or more of minority women. This is in addition to three Vanguard Clinical Centers which are already recruiting 60 percent or more minorities. Interest in joining the clinical trial is high, and currently over 5,000 women have enrolled in the study.

The design of strategies for implementation of the Community Prevention Study, to enhance adoption of healthful behaviors, is still under review. There exist many behaviors of proven value to improving women's health, but these behaviors have not been widely adopted. Special emphasis will focus on minorities, the medically underserved, and the socioeconomically disadvantaged populations in these communities. The request for applications will be released in FY 1995.

Minority Health Initiative

The Minority Health Initiative (MHI) is the centerpiece of the research agenda of the Office of Research on Minority Health (ORMH). The budget request for the MHI is $62,797,000, an increase of $4,500,000. Research on minority health is an NIH priority because minority Americans are disproportionately affected by a wide range of diseases and are under-represented in biomedical research careers. The MHI builds on previous NIH efforts to improve the overall health of minorities and to train more minority biomedical researchers. The MHI comprises a portfolio of multi-year research projects as collaborative efforts with NIH ICDs as well as new components developed to confront emerging and unaddressed health research areas.

The Infant Mortality component of the MHI supports community-based epidemiologic and clinical research to address the problem of the unacceptably high infant mortality rate in inner cities, including Washington, D.C. Three studies--involving parenting education, immunization rates, and health services evaluation--were initiated in FY 1994. An additional five protocols are under development. This component is funded at $5,000,000 for FY 1995 and an estimated $3,000,000 for FY 1996.

The Minority Children component focuses on research on injury-related morbidity, lead poisoning, asthma, learning disorders and hearing and speech impairments among minority children ages 1-9. This component includes a major research initiative, begun in FY 1994, to address the etiology and treatment of a variety of environmentally-related health problems in minority children, including Toxicity of Lead in Children Clinical Trial and the Study of Biokinetics of Lead in Primate and Human Pregnancy, both of which are collaborative activities with the National Institute of Environmental Health Sciences (NIEHS). This component if funded at $5,000,000 for both FY 1995 and FY 1996.

The Minority Youth Initiative focuses on the development and evaluation of community-based interventions for decreasing violence-related injuries and deaths, sexually transmitted diseases and unintended pregnancies in minority youths, aged 10-24. This component is funded at $5,000,000 for FY 1995 and an estimated $3,000,000 for FY 1996.

The Young Adult Initiative supports a variety of research projects related to the health problems and behaviors of young minority adults. Research projects focus on problems such as kidney disease, diabetes, hemochromatosis, glaucoma, lupus, AIDS and alcoholism,--including risk factors for alcoholism in Native Americans. Three projects were initiated in FY 1994: Gene/Environment Interactions in American Indian Tribes with Low and High Rates of Alcoholism (in collaboration with the National Institute of Alcoholism and Alcohol Abuse); Primary Prevention of Non-Insulin Dependent Diabetes in Minorities (in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and Eye Disease in Native Americans (in collaboration with the National Eye Institute). These programs are funded at $6,000,000 for FY 1995 and an estimated $6,800,000 in FY 1996.

In collaboration with the National Institute on Aging, MHI funds Exploratory Centers for Research on Health Promotion in Older Minority Populations. This program supports and coordinates a series of research projects relating specifically to issues of aging of minorities and provides increased opportunities for involvement of minority investigators in research on aging. The funding level for this component is $2,000,000 for both FY 1995 and FY 1996.

The following new initiatives begin to address emerging areas of research: the HIV/Minority Adolescent Community Initiative (in collaboration with the National Cancer Institute); Research on Genetic Causes of Diabetes (in collaboration with NIDDK); Environmental Justice Research Center grants (in collaboration with NIEHS); and the Neurological Sciences Center (in collaboration with the National Institute of Neurological Disorders and Stroke); the Heart Education and Research Translation (HEART) Project (in collaboration with the National Heart, Lung and Blood Institute). Each of these programs results from extensive interactions between the ORMH and the collaborating ICDs.

The MHI supports a collaboration between the National Science Foundation (NSF) to expand and emphasize the biomedical components in established NSF science programs in middle schools, high schools, and colleges. This collaboration will continue during FY 1996. These programs are funded at $2,500,000 for FY 1995 and an estimated $2,000,000 for FY 1996.

MHI funds also supported the Administration's bilingual/bicultural service demonstration program, which aims to improve access to health services among minority populations with limited English-speaking capability. Additionally, MHI funding strengthened the capacity of historically black colleges and universities (HBCUs) to provide quality education, to participate in and benefit from Federal programs, and to obtain increased support from the private sector.

In FY 1996, many new areas of concern and interest to the minority biomedical community will be addressed in response to the National Conference on Minority Health Research and Research Training, held in Chicago, Illinois in March, 1994. The ORMH will encourage the NIH ICDs to collaborate broadly across the government. This may allow new ORMH programs to be initiated.

One new program will be research on the effects of migration on health. Since much of the recent growth in the various minority populations is a result of migration to the United States, which can markedly change a person's living conditions, diet and socioeconomic status, all of these changes can impact on the health status of such populations. Due to the difficulties of researching such a transient population, the NIH will collaborate with the community-based organizations that provide health services to migrant workers. Another area of research will be the health and behavioral effects of childhood lead exposure in inner city neighborhoods and studies of additional health conditions, particularly those of the U.S.-Mexico border.

A final major area of concern is the health of minority women. A variety of women's health issues will be funded in collaboration with ORWH, including reproductive health, mental health during pregnancy and the effects of poor mental health on both mothers and children, and the health of post-menopausal women. The ORMH initiative will support, minority research training efforts in the development of Centers of Excellence at those minority institutions that are long-time beneficiaries of NIH infrastructure support. The ORMH will initiate and provide partial support for research/training partnerships based at minority institutions and initiate training activities that respond to the needs of minorities at every stage of their educational or professional development. In addition, the ORMH will develop an outreach program and a database to disseminate information regarding NIH minority health research and minority training programs, and a list the research interests and capabilities of both individual minority scientists and minority institutions and community-based organizations, respectively.

Training components will also be expanded in the MHI. The Bridges to the Future program provides linkages for minority students between two-year junior or community colleges and four-year colleges and between terminal M.S. degree programs and Ph.D. programs. The Bridges program will be funded at $9,000,000 for FY 1995 and an estimated $11,000,000 for FY 1996. The Research Centers in Minority Institutions program provides a fertile research environment for students and faculty of minority institutions. Fund for this program in FY 1995 is $4,000,000 and an estimated $4,000,000 for FY 1996. The Minority International Research Training (MIRT) is a new initiative which will support research and research training of students and minority faculty at the international level. Funding for this program in FY 1995 is $6,000,000 and an estimate $6,000,000 for FY 1996. The ORMH is collaborating with the National Science Foundation (NSF) to expand and emphasize the biomedical components of middle school, high school and college science programs.

Research on Women's Health

The ORWH serves as the focal point within the NIH to develop and implement an agenda for research on women's health, to ensure that women are appropriately represented in biomedical and behavioral research studies supported by NIH, and to develop opportunities and support for recruitment, retention, re-entry and advancement of women in biomedical research careers.

The research agenda, first defined in FY 1991 based upon an expanded concept of women's health across the life span and addressing conditions both unique to women as well as those that affect men and women, is dynamic and responsive to evolving science. Because of the broad scope of identified gaps in knowledge related to women's health, each year the ORWH determines major areas to be targeted for emphasis utilizing three major strategies for stimulating such research: 1) targeted research, 2) supplements to ongoing projects, and 3) special initiatives.

The ORWH has targeted research in four major areas: women's urological health, reproductive health and sexually transmitted diseases, autoimmune diseases, and occupationally-related diseases and disabilities. For example, ORWH has joined with the NIH ICDs to support research on urinary bladder physiology, the mechanisms underlying endometriosis and fibroid initiation and growth, the natural history of menopause, the etiology of and pathogenic mechanisms involved in autoimmune disease, and tissue and cellular response to silicone polymers. ORWH focused its supplement program on eleven specific areas of women's health that have had insufficient research attention. In addition to the targeted areas, these included studies on lung cancer, risk factors for disease among women of different racial and ethnic groups, the molecular basis for gender differences in disease manifestations, cardiovascular disease, behavioral and cultural factors related to women in regards to disease risk and intervention, including violence and substance abuse, and depression and its interaction with other health problems. In FY 1994, ORWH made 76 supplemental awards to ongoing research; 58 percent were directed toward clinical research, 42 percent toward basic research. ORWH collaborated with NIH ICDs to co-fund several special initiatives including study of gender differences in immune response, and the study of disabilities in women as they age. The ORWH participated in the planning, development and financial support of the Secretary's (DHHS) Conference on Breast Cancer, which brought together scientists, breast cancer survivors and patients, and representatives of the advocacy and media communities in a collaborative effort which resulted in a plan to eradicate breast cancer. This plan is now being implemented by the Secretary through the Administration's Office of Women's Health. ORWH supported other research conferences and workshops to assist in updating the scientific research agenda on women's health, as Congressionally mandated, including workshops on temporomandibular joint disease with a particular focus on joint implants, chronic fatigue syndrome, urological health, environmental risks for osteoporosis, and sexually transmitted diseases.

The ORWH continues to monitor clinical studies funded by NIH regarding the inclusion of women. In response to the NIH Revitalization Act of 1993, ORWH, in collaboration with other offices within the Office of the Director, issued a revised policy on Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. This new policy substantially extends the 1990 NIH policy and requires the inclusion of minority subpopulations, outreach to underrepresented populations, and valid analyses of gender and racial/ethnic differences arising from Phase III clinical trials. In response to the legislation, ORWH participated in efforts to familiarize NIH staff with the new requirements; made presentations at national meetings about the revised policy; and prepared and disseminated "The NIH Notebook on Inclusion of Women and Minorities in Clinical Research." The ORWH has published the report of its public hearing and scientific workshop on the "Recruitment and Retention of Women in Clinical Studies", which will provide investigators with innovative and proven methods to assist in achieving appropriate representation of women and minorities in clinical trials. The ORWH contract with the Institute of Medicine, in response to a Congressional directive as well as a need for better information related to concerns about the inclusion of women of childbearing age in clinical research, resulted in a widely acclaimed report entitled, "Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies". The report now serves as a basis for NIH and other Administration agencies to reexamine policies and investigative studies related to women's health across the lifespan. The ORWH joined with the FDA in sponsoring a workshop, "FDA Regulated Products and Pregnant Women," to bring together health care providers, scientific investigators, consumers, industry and government groups to identify and debate medical, ethical, and legal issues relating to clinical trials in pregnant women.

The workshop report, "Women in Biomedical Careers", identified many opportunities for the recruitment, retention, reentry and advancement of women in medical research. A pilot program, developed by ORWH to aid in the reentry of scientists who left their careers due to family responsibilities, was adopted by 15 ICDs in FY 1994 for their extramural programs. The intramural reentry program, designed to develop a self-perpetuating core of researchers, professors, and teachers who will serve as role models and mentors in attracting and guiding women and minorities into scientific careers, has designated three scientists in several NIH laboratories. ORWH also supports opportunities for high school students to learn about science from NIH scientists through lectures and laboratories at the NIH campus and to encourage them to pursue careers in science. In an effort to reach out broadly, ORWH and the Office of Science Education have developed a section on EDNET to provide information about various ORWH career development and research activities.

The budget request for ORWH is $17,250,000, an increase of $4,500,000 over the FY 1995 estimate. This increase will enable the ORWH to continue to refine and expand its programs and activities in women's health research, inclusion of women in clinical research, and women's biomedical career development. The partnerships that the ORWH has established both within and outside the NIH will continue and will be enhanced as new opportunities are identified.

The ORWH will develop new collaborative initiatives to address continuing gaps in knowledge about women's health which affect both mortality and morbidity. The research agenda will identify newly evolving areas of women's health not previously defined or recognized. The ORWH will continue to direct attention to a number of efforts required by the legislation on the inclusion of women and minorities in clinical research. Priorities will be the continued development of outreach programs to increase the recruitment and retention of women in clinical trials and training regarding the implementation of the new inclusion guidelines. The tracking system will be modified to assist in monitoring inclusion under the revised guidelines. Recommendations from the ORWH report on women in biomedical careers will be implemented.

Research on Minority Health

In addition to providing administrative support for the MHI, the Office of Research on Minority Health (ORMH) will place special emphasis on the following areas in FY 1996: expansion of technical assistance workshops which will allow minority scientists to interact with ICD staff regarding the preparation of grant applications; plans to address by convening the health concerns of each ethnic group separately as supported in Healthy People 2000 a conference to focus on Asians and Pacific Islanders in FY 1995; coordination of supplemental programs; and outreach and liaison activities and support. The budget also supports a contract to develop a strategic plan to educate minority Americans about the importance of organ donation. This strategy is being implemented in 11 cities nationwide and will involve an impact on all major minority groups--Native Americans, Asian/Pacific Islander Americans, Hispanics, and African Americans.

The budget also supported the implementation of Phase II of an ongoing assessment of NIH minority training programs. This assessment was recommended by the 1991 FFT. Phase I, a presentation of available information and trend data for existing NIH minority research and training programs, was completed in FY 1993. Phase II is a planning phase, involved in implementing a feasibility study to design a prospective assessment of NIH minority research and training programs. Phase III, the implementation of the assessment will start in FY 1995 and will be completed in FY 1996.

The FY 1996 request for the Office of Research on Minority Health is $9,433,000, an increase of $491,000. This budget funds all of the support activities and operational costs of the Minority Health Initiative. In part, the increase will provide for additional support for technical assistance programs, outreach and liaison activities and a contract involved in the implementation of an assessment and tracking system of NIH minority research training programs. The ORMH also continues to educate the minority community about important NIH policies and programs, including the guidelines regarding inclusion of women and minorities in research.

Science Education

The Office of Science Education Policy (OSEP), during 1994 lead, directed, and coordinated science education policy for the Department, the PHS, and NIH. It is the focal point for DHHS involvement in the National Science and Technology Council Committee on Education Training (NSTC/CET) and provides leadership for the Adminstration's Life Sciences Education and Science Literacy Board. The office is also active in the development of innovative science education programs that address areas and audiences typically overlooked in traditional research training programs. These programs include: the Biomedical Research Advancement: Saturday Scholars (BRASS) program, a Saturday morning science education program for local 7th grade students; the Science Education Partnership Awards (SEPA) program, a grant program encouraging the development of creative partnerships between educators and researchers (through the NCRR); and two new programs for the general public--the NIH Mini-Med School and the Science in the Cinema film festival. These programs will be continued in FY 1996.

In addition to its continued support of the NSTC/CET, the PHS Board, and a number of ongoing NIH science education efforts, OSEP performed a pilot test of the BRASS program in Boston and Tennessee, developed and further refined the BRASS curriculum for a wider dissemination, awarded funds to grants to provide follow-up funding for the most successful SEPA projects, and set up pilot programs for the NIH Mini-Med School and the Science in the Cinema programs. The NIH Mini-Med School was a nine week program which allowed 280 members of the general public to experience some of the same courses as "real" medical students. This program was very popular and generated over 1,300 requests for enrollment. Science in the Cinema was a four week summer program for the general public in which popular theatrical films (e.g. Awakenings and Lorenzo's Oil) were first shown and then discussed by guest scientists who commented on the film's scientific accuracy as well as providing additional insights.

Office of Alternative Medicine

During FY 1994 the Office of Alternative Medicine (OAM) conducted a number of successful workshops, including a landmark meeting in conjunction with the Food and Drug Administration (FDA) on the use of acupuncture needles. This led to the submission of a citizens' petition to FDA for the reclassification of such needles to remove them from the device category. Twelve additional small exploratory grants were awarded. Important precedents were set as OAM grantees obtained permission to begin human studies with three herbal products and one homeopathic remedy, with the FDA accepting the lack of reported problems from human experience in lieu of animal toxicity data. Two new exploratory research centers were funded under cooperative agreements to assist alternative practitioners to document their therapies with prospective studies in the treatment of HIV infection and substance abuse disorders. The HIV award was a milestone in NIH history, being the first NIH award ever to a Naturopathic institution.

During FY 1995, a new Director of OAM will be appointed and the goals of the OAM for FY 1996 will expand and may include: the funding of two more national exploratory centers, one to serve as a national resource center for research on alternative therapies for pain, and one to serve as a national resource for research on alternative approaches to enhancing health for those who are chronically ill; as well as those who are well; the establishment of a postdoctoral training program in the clinical epidemiology of alternative therapies; exploration of establishing interagency agreements with one or more federal programs with large general patient populations to set up one or more clinical trials of alternative therapies in outpatient populations.

Academic Research Enhancement Award Program

The purpose of the Academic Research Enhancement Award (AREA) program is to provide an opportunity for faculty in educational institutions that are not research-intensive to participate in the nation's biomedical and behavioral research effort. AREA grants provide support of new or expanded health-related research projects at undergraduate educational institutions primarily, at which a significant number of America's research scientists receive their college education. In FY 1994, 130 AREA awards, amounting to $13,234,000, were issued, as compared to 127 AREA awards totaling to $12,900,000 for the previous year. In FY 1996 the Academic Research Enhancement Award Program (AREA) has been identified as a NIH Emphasis Area. The budget request for AREA is $14,092,000, an increase of $1,396,000. With the additional funding AREA will be able to make approximately 13 additional awards.

Loan Repayment and Scholarship Programs

In FY 1994, through the loan repayment and scholarship programs authorized under the NIH Revitalization Act of 1993, the NIH awarded $210,778 to five individuals under its Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (CR-LRP). The awardees agreed to conduct clinical research as employees of the NIH for a minimum period of two years, while the NIH agreed to provide repayment of their educational loan debt, subject to a maximum of $20,000 annually. The NIH began development of an Undergraduate Scholarship Program (UGSP) to provide scholarships to individuals from disadvantaged backgrounds. Awards will be made to undergraduate students who agree to pursue academic programs suitable for careers in professions of importance to the NIH. Scholars would agree to work at the NIH for one year for each year of scholarship support after graduation. For FY 1995, the CR-LRP and the UGSP will each award contracts to 10 individuals at costs of $330,500 and $200,000, respectively.

In FY 1996 the request includes $2,963,000, an increase of $2,032,000. The Loan Repayment and Scholarship Programs have been identified collectively as a NIH Emphasis Area in FY 1996. The additional funding will be used for 13 awards under the Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds, 12 for the Undergraduate Scholarship Program, and 20 awards for a new General Research Loan Repayment Program (GEN-LRP).

The GEN-LRP will award contracts to physicians and scientists engaged in both basic and clinical research activities at the NIH. This program is intended to recruit and retain health professionals to non-trainee NIH positions; thus, such individuals will be considered for permanent and/or tenure-track positions. GEN-LRP participants agree to a minimum contract period of three years. In addition to educational loan repayments, the GEN-LRP provides Federal tax reimbursements at the rate of 39% of loan repayments made as compensation for the increased Federal tax burden resulting from the receipt of loan repayments.

Office of Behavioral and Social Sciences Research

The mission of the Congressionally mandated Office of Behavioral and Social Sciences Research (OBSSR) is: to provide the leadership and direction for the development, coordination, refinement, and implementation of an overall NIH research strategy for the conduct and support of behavioral and social science research; and to educate the biomedical community and the general public about the role of individual, familial, social and environmental factors in the promotion of good health and the prevention, treatment, and cure of disease.

A permanent OBSSR Director and staff will be in place in FY 1995 to provide a prominent focus within the NIH for the coordination of biobehavioral research initiatives. The order of business will be to develop a standard definition of behavioral and social science research initiatives; and to promote multidisciplinary research in these areas. In FY 1996 approximately $2,000,000 will be used to supplement ICD research and training programs to foster the integration of behavioral, social science, and biomedical research and the remaining funds will be used for program support.

Director's Discretionary Fund

The Director's Discretionary Fund (DDF) enables the Director, NIH, to be more responsive to emerging research opportunities and health priorities. During FY 1994 the DDF provided $4,120,000 to support 103 Shannon Awards, $1,950,000 to support research through the Decade of the Brain initiative, $124,000 to the National Cancer Institute (NCI) to support the NCI RFA entitled "Cloning and Sequencing the BRCA1 Gene", and $90,000 to support partial funding of the two-year contracts for five approved participants in the Clinical Research Loan Repayment Program. Projects for FY 1995 and FY 1996 have not yet been identified.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of Director 1/.....	700	705	686

Average GS/GM Grade

1991	10
1992	10
1993	10
1994	11
1995	11
1996	11

1/ Includes 57 FTEs in FY 1994, 65 FTE's in FY 1995 and 66 FTEs in FY 1996 associated with AIDS Research Activities.

DHHS - NATIONAL INSTITUTES OF HEALTH
Detail of End-of-Year Employment
Office of the Director

	1994 Actual	1995 Estimate	1996 Estimate
Executive level IV	1	1	1
Total - Exec. Lev. Sal	148,400	154,350	160,500
ES-6	2	2	2
ES-5	5	5	5
ES-4	6	9	9
ES-3	1	1	1
ES-2	0	1	1
ES-1	0	0	0
Subtotal	14	18	18
Total - ES Salary	1,536,000	2,062,000	2,145,000
GS/GM-15	40	45	44
GS/GM-14	71	80	78
GS/GM-13	121	124	121
GS-12	91	94	91
GS-11	35	36	35
GS-10	10	10	10
GS-9	37	38	37
GS-8	25	26	25
GS-7	87	89	86
GS-6	29	30	29
GS-5	24	25	24
GS-4	7	7	7
GS-3	1	1	1
GS-2	0	0	0
GS-1	0	0	0
Subtotal	578	605	588
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	14	14	14
Senior Grade	4	4	4
Full Grade	1	1	1
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	19	19	19
Ungraded	59	62	60
Total permanent positions	671	705	686

164

Total positions, end-of-year..........	671	705	686
Total full-time equivalent (FTE) employment, end of year.............	700	705	686

Average ES level.................	5	5	5
Average ES salary................	109,550	111,908	114,146
Average GS/GM grade..............	11	11	11
Average GS/GM salary.............	44,041	45,142	46,270

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Building and Facilities

FY 1996 Budget	Page No.
Appropriation language	100
Amounts available for obligation	101
Summary of changes	102
Budget authority by object	103
Significant items in House and Senate Appropriations Committee reports	104
Authorizing legislation	105
Appropriation history	106
Budget authority by project	107
Justification:	
A. General statement	109
B. Program activities	112

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

For the study of, construction of, and acquisition of equipment for, facilities of or used by the National Institutes of Health, including the acquisition of real property, [$114,120,000] *$144,120,000*, to remain available until expended. *(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1995, P. L. 103-333.)*

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation [1/]

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation.............	$111,039,000	$114,120,000	$144,120,000
Unobligated balance, start of year...........	198,949,000	226,659,000	---
Unobligated balance, end of year.............	-226,659,000	---	---
Total obligations....	83,329,000	340,779,000	144,120,000

[1/] Excludes the following amounts for reimbursable activities carried out under this account: FY 1994 -- $2,640,000, FY 1995 -- $5,100,000.

Buildings and Facilities

Summary of Changes

1995 Estimated budget authority	$114,120,000
1996 Estimated budget authority	144,120,000
Net change	+30,000,000

	Change from Base Budget Authority
Increases:	
A. Program:	
1. Clinical Center Essential Maintenance & Safety	+$1,000,000
2. Infrastructure Modernization Program	+361,000
3. Eliminate Barriers to Persons With Disabilities	+1,500,000
4. Safety and Reliability Upgrades, RML	+2,700,000
5. Indoor Air Quality Improvement Program	+1,500,000
6. New Fire Station	+5,570,000
7. Clinical Center Complex Renewal Program	+23,000,000
8. Consolidated Laboratory Building	+32,723,000
9. Repairs and Improvements	+2,046,000
10. Turner Construction Claims, NIEHS	+400,000
Total increases	+70,800,000
Decreases:	
A. Program:	
1. Medical Pathological Waste Management System	-$3,500,000
2. William H. Natcher Building	-30,800,000
3. NIEHS Additions to Facilities	-4,000,000
4. Clinical Center Review	-2,500,000
Total decreases	-40,800,000
Total, Net Change	+30,000,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Other services	$114,120,000	$144,120,000	$+30,000,000
(Obligations)	340,779,000)	(144,120,000)	(-196,659,000)
Total budget authority by object	114,120,000	144,120,000	+30,000,000
(Total obligations by object)	(340,779,000)	(144,120,000)	(-196,659,000)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1995 House Report	
Intramural Research Program	
1. The House in its report 103-553, page 68, stated, "The Committee encourages the Director to implement suggested reforms as expeditiously as possible. In particular, the Committee encourages NIH to present a plan as quickly as possible for the renovation of a down-sized but state-of-the-art research hospital to replace the aging clinical center facility. This plan should include specific recommendations for the reallocation of existing resources, including intramural resources, to partially finance the cost of this facility".	1. A report is being prepared by the Office of the Director, Office of Intramural Research, and will be forwarded to the Committee shortly.
Review of Facility Needs	
2. The House in its report 103-553, page 71, stated, "The Committee expects the Director of NIH to review facility needs and report to the committee his views regarding necessary changes in the facilities program".	2. A report is being prepared and will be forwarded to the Committee shortly.
1995 Senate Report	
Intramural Research Program	
1. The Senate in its report 103-318, page 114, stated, "The Committee encourages the Director to implement the suggested reforms, and requests the NIH to plan a plan for the renovation of a downsized research hospital to replace the existing clinical center. That plan should also include a proposal for financing the cost of this facility, to the maximum extent possible, by reallocating existing resources".	1. Same response as number 1 in "1995 House Report".

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Funded Authorizations:						
Buildings and Facilities............	Title IV, Section 402(b)	40§282	Indefinite	$114,120,000	Indefinite	$144,120,000
Total Budget Authority..				114,120,000		144,120,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$8,000,000	$31,900,000	$31,900,000	$31,900,000
1988	5,000,000	30,000,000	50,000,000	47,870,000
1989	5,000,000	20,000,000	12,500,000	38,532,000
1990	21,600,000	81,600,000	41,600,000	61,600,000
1990 Sequester				-558,000
1991	86,903,000	239,903,000	68,803,000	168,687,000 2/
1991 Sequester				-2,000
1992	104,125,000	108,625,000	89,485,000	103,840,000
1993	72,518,000	70,090,000	59,222,000	108,731,000
1994	108,731,000	114,385,000	101,000,000	111,039,000
1995	113,539,000	114,370,000	113,370,000	114,120,000
1996	144,120,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes enacted administrative reduction of $4,166,000.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Project
(Dollars in thousands)

	1994 Actual	1995 Appropriation	1996 Estimate	Change
Clinical Center Essential Maintenance and Safety Program	$20,900	$20,000	$21,000	+$1,000
Infrastructure Modernization Program	13,485	13,439	13,800	+361
Power Plant Improvements	2,000	2,000	2,000	---
Asbestos Abatement Program	5,500	5,500	5,500	---
Fire Protection and Life Safety Program	2,000	2,000	2,000	---
Eliminate Barriers to Persons With Disabilities	---	---	1,500	+1,500
Safety and Reliability Upgrades, RML	1,000	2,000	4,700	+2,700
Medical Pathological Waste Management System	---	3,500	---	-3,500
Indoor Air Quality Improvement Program	---	---	1,500	+1,500
New Fire Station	---	---	5,570	+5,570
Clinical Center Complex Renewal Program	---	---	23,000	+23,000
Consolidated Laboratory Building	---	---	32,723	+32,723
William H. Natcher Building	27,500	30,800	---	-30,800
Repairs and Improvements	17,854	17,381	19,427	+2,046
NIEHS Additions to Facilities	12,000	10,000	6,000	-4,000
Turner Construction Claims, North Carolina	5,000	5,000	5,400	+400
Clinical Center Review	---	2,500	---	-2,500
Cell Biology Facility	3,800	---	---	---
Total budget authority	111,039	114,120	144,120	+30,000
Unobligated balance, start of year	198,949	226,659	---	-226,659
Unobligated balance, end of year	-226,659	---	---	---
Total obligations	83,329	340,779	144,120	-196,659

Justification

Buildings and Facilities

	1994 Actual	1995 Appropriation	1996 Estimate	Increase or Decrease
Total budget authority.	$111,039,000	$114,120,000	$144,120,000	+$30,000,000
Total obligations......	(83,329,000)	(340,779,000)	(144,120,000)	(-196,659,000)

General Statement

This appropriation provides for the design, construction, improvement, and major repair of clinical and laboratory buildings and supporting facilities essential to the mission of the National Institutes of Health. Funds are provided for non-recurring direct construction projects as well as ongoing major repairs and improvements. All funds are available until expended.

Construction of facilities for the National Institutes of Health spans a period of nearly 59 years, dating back to legislation that authorized Building 1 in June 1936. Facilities funded under this appropriation include those required for both research programs and support services at the main NIH Reservation in Bethesda, Maryland, totaling 77 buildings and more than seven million gross square feet of space. Additional facilities are the Frederick Cancer Research and Development Center, Frederick, Maryland; the National Institute of Environmental Health Sciences (NIEHS) facility in Research Triangle Park, North Carolina; the Gerontology Research Center, Baltimore, Maryland; the NIH Animal Center located in Poolesville, Maryland; the Rocky Mountain Laboratory, Hamilton, Montana; and Primate Facilities at Perrine, Florida, New Iberia, Louisiana, and Sabana Seca, Puerto Rico.

The NIH is developing updated master plans scheduled for completion in FY 1995, for both the Bethesda campus and the NIH Animal Center in Poolesville. Significant growth on and off the NIH sites, the aging of the facilities and infrastructure, the development of new technologies, and the evolving biomedical research programs at NIH have rendered the existing plans of more than two decades nearly obsolete. The new comprehensive master plans will identify programmatic requirements in terms of personnel and physical facilities; establish concepts for future development and land use, buildings, utilities, open space, circulation and traffic management at both sites for the next twenty years; and illustrate how needs for laboratory and clinical research, administrative, and support space can be achieved.

The NIH is contending with an aging, deficient physical plant. The majority of the infrastructure systems are 20 to 40 years old, undersized, and beyond their design life. To address these deficiencies and plan for the future, the NIH is integrating all corrective and new construction programs into a comprehensive Facilities Revitalization Program. The intent of this program is to develop a long-term strategy to coordinate programs and set priorities so that ongoing laboratory and clinical research as well as anticipated technological advancements and program growth can be supported in accordance with modern standards.

The NIH has placed a high priority on the renewal of the Clinical Center Complex. The Clinical Center Complex contains approximately 40 percent of the research space on the Bethesda campus and is the keystone of the NIH Intramural Research Program. The utility systems within the complex are old, outmoded, obsolete, and insufficient to support modern research. The NIH has developed plans to renew the complex consistent with the recommendations contained in the External Advisory Report, The Intramural Research Program. Plans for the Clinical Center Complex have been detailed under Program Activities.

Equally, the NIH gives a high priority to safety and health requirements. Infrastructure upgrades to existing NIH facilities are necessary to meet critical occupational and environmental requirements to protect and support ongoing research programs, including the safety and health of NIH employees and patients. This is the purpose of the Essential Safety and Health Improvement initiative. Supporting utilities should be modernized and improved to meet safety and health requirements to support the NIH research mission.

Purpose and Method of Operation

Funding for Buildings and Facilities during the last 5 years has been as follows:

Year	Amount
FY 1991	$167,341,000
FY 1992	101,840,000
FY 1993	108,731,000
FY 1994	111,039,000
FY 1995	114,120,000

The Buildings and Facilities appropriation funds two major requirements of the NIH biomedical research mission: the design and construction of new facilities for NIH research programs and the continuing renovation, alteration, maintenance, and repair of existing facilities. Long-term projects currently under construction include campus infrastructure modernization, modernization/safety upgrades of the NIH Clinical Center, rehabilitation of the campus' oldest laboratory buildings, the asbestos abatement program, and the renovation of existing animal facilities. Initial construction for replacement of leased facilities at the National Institute of Environmental Health Sciences began in December 1992.

Overall Budget Policy

The 1996 budget request of $144,120,000 reflects the high priority placed on safety and health requirements necessary to meet critical infrastructure and environmental improvements to the existing facilities to protect and support ongoing research programs. The enhanced program for essential safety and health improvements includes funding for the upgrade or replacement of essential equipment and systems to keep the Clinical Center safely operational; the site infrastructure modernization program; the continuation of programs for power plant safety, asbestos abatement, fire protection and life safety, the elimination of barriers to persons with disabilities, and safety and reliability upgrades at the Rocky Mountain Laboratory; implementation of an indoor air quality improvement program; and construction of the new fire station. Funds are included for an initial portion of the design and construction quality management during design for the hospital and laboratory addition of the Clinical Center and the completion of construction for the Consolidated Laboratory Building. The request also provides for continued funding for the replacement facilities at the NIEHS, the final annual payment related to the Turner Construction Company claim settlement, and funding for ongoing repair and improvement of facilities.

Buildings and Facilities

Program Activities

Authorizing Legislation - Section 402(b) of the Public Health Service Act.

Budget Authority:

1994 Actual	1995 Appropriation	1996 Estimate	Increase or Decrease
$111,039,000	$114,120,000	$144,120,000	+$30,000,000

Rationale for the Budget Request

The FY 1996 budget request for Buildings and Facilities is $144,120,000, an increase of $30,000,000 over FY 1995. The basic thrust of the 1996 budget request is the program of essential safety and health improvements required to meet critical infrastructure and environmental improvements to existing NIH facilities in order to protect and support ongoing research programs.

Essential Safety and Health Improvements

FY 1996 Budget Request.. $57,570,000

1. Clinical Center Essential Maintenance and Safety Program

FY 1996 Budget Request.. $21,000,000

The Clinical Center Essential Maintenance and Safety (EMS) Program provides for the urgently needed restoration of the existing primary building utility systems and the correction of life safety problems to keep the Clinical Center safely operational for the next 12 to 15 years. Extensive alterations are necessary to comply with safety requirements and allow modern procedures, equipment, and facilities to provide quality patient care and supporting research. The EMS Program will focus on safety issues, hospital accreditation, and major central system renovations to enhance reliability of a facility over 40 years old. This request is the third year of a multi-year program and will provide for the initial replacement of mechanical/electrical systems distributed throughout the building. This program represents the minimum investment necessary to maintain the functionality and safety of the existing Clinical Center while the renewal program is carried out.

2. Infrastructure Modernization Program

FY 1996 Budget Request.. $13,800,000

This request is the sixth year of the nine-year effort for the replacement and expansion of central utility equipment and distribution systems. The majority of the NIH Central Utility Plants and distribution networks are over 40 years old. Obsolescence and system deteriorations due to age, overburdening from growth, and increases in program needs have produced a critical situation where sufficient and uninterrupted services to research and patient care activities can no longer be ensured. The possibility of catastrophic failure has become very real, and the current situation could encumber or destroy the capability to carry out the NIH mission.

To correct this, a programmed restoration, renovation, replacement, and expansion of the mechanical and electrical utility systems has been developed. Specific central utility services include chilled water, steam, electrical power, compressed air, domestic water, sewerage, and natural gas. Equipment includes chillers, boilers, control and monitoring systems, pumps, switchgear, and other ancillary apparatus. Facility accommodations include the necessary conversion, expansion, or creation of mechanical and electrical system spaces, as well as any program relocations which are a result of this effort.

This increment will include replacing and/or enhancing specific central utility equipment and systems which have been identified as mandatory to maintain current campus-wide operations. Work of this phase will include expansions of the refrigeration building and utility distribution tunnels, design for a new chiller, and design and reconditioning of three boilers.

3. Power Plant Improvements

FY 1996 Budget Request.. $2,000,000

This program provides for the necessary modifications to the NIH Power Plant to enable continuing emissions compliance with National Ambient Air Quality Standards. This is the third year of a five-year program for upgrading the NIH Power Plant, Building 11, to maintain and improve emissions in compliance with acceptable air quality standards. This request will provide for the continuation of implementing long-term reduction measures, in addition to removal of hazardous materials from within the Power Plant.

4. Asbestos Abatement Program

FY 1996 Budget Request.. $5,500,000

This project provides for the continued phased removal of asbestos containing materials from various NIH buildings. Insulation, fireproofing, and ceiling and wall finishes containing asbestos are present in virtually all NIH buildings. Disturbed or deteriorating asbestos fibers can be released into the air, risking the health of those persons exposed. Asbestos control practices are instituted whenever there is a risk of exposure to significant airborne asbestos concentrations. This is the third year of a ten-year program.

5. Fire Protection and Life Safety Program

FY 1996 Budget Request.. $2,000,000

Funding is requested for the third year of a multi-year program to upgrade the fire protection and life safety equipment of NIH buildings on the campus and at the NIH Animal Center. Significant deficiencies exist which compromise NIH's ability to provide adequate protection to all persons using or working in NIH facilities as well as protection of critical research facilities and resources. A master fire protection plan is under development as part of the program. Fire sprinklers and an improved alarm and reporting system will be installed as well as improvements in emergency egress.

6. Eliminate Barriers to Persons With Disabilities

FY 1996 Budget Request.. $1,500,000

This project involves the systematic removal of existing barriers within the NIH buildings. A survey of NIH buildings has been completed which identifies access barriers as well as remaining architectural barriers. Items that still need modification, such as additional restrooms, elevator controls, door openings, and fire alarm devices are being developed in concert with the NIH Employees with Disabilities Committee. Eliminating barriers in exterior situations has been largely satisfied, or are in progress. The funds required in FY 1996 provide for a continuation of this program by addressing interior barriers.

7. Safety and Reliability Upgrades, Rocky Mountain Laboratory

FY 1996 Budget Request.. $4,700,000

Funds are requested to support the major portion of the third year of a five-year program to upgrade the existing main laboratory complex at the Rocky Mountain Laboratory (RML) in Hamilton, Montana, to be compliant with current fire/life safety standards for biomedical research facilities. Specifically, this project includes the replacement of piping; addition of heating, ventilation, and air conditioning systems; increase in electrical services; installation of a fire sprinkler system throughout the complex; and other modifications required for code compliance and accessibility. These funds will provide for the upgrade of all six buildings of the main laboratory complex and the completion of life safety and utility upgrades of the other laboratory buildings.

8. Indoor Air Quality Improvement Program

FY 1996 Budget Request.. $1,500,000

This is the initial request to begin the study, design, and construction of a multi-year program to fully address indoor air quality concerns at NIH facilities. This program will allow for the evaluation of existing structures and ventilation facilities to determine the total need for system upgrades or replacements. Items of concern to be evaluated include heating, ventilation, and air conditioning system capacity; relative air flow; fume hood operation; recirculated air quality; sources of contamination; and potential cross-contamination. A comprehensive program will be developed to fully address the indoor air quality requirements.

9. New Fire Station

FY 1996 Budget Request.. $5,570,000

This request provides for construction of a new fire station for the NIH at the Bethesda campus. The existing station, built in 1949 as a garage and maintenance facility, is inadequate for the present needs of the NIH. The new facility will provide approximately 22,900 gross square feet (gsf) of space. In order to accommodate a fire station, the facility will contain an apparatus room for seven emergency response vehicles with the capability to accommodate one additional vehicle in the future. The facility will also provide space for dormitories, offices, a communication area, training areas, and storage.

Clinical Center Complex Renewal Program

FY 1996 Budget Request..$23,000,000

The Clinical Center Complex (CCC) at the NIH has been one of the most unique facilities and valuable resources for the conduct of clinical research anywhere in the world. It is the keystone of the NIH intramural program. The original size of the Warren Grant Magnuson Clinical Center was approximately 1.3 million gsf. Through a number of additions over the years, the Clinical Center has grown into a complex of approximately 3.0 million gsf. The evolution of the CCC over the past 40 years has resulted in utility infrastructure systems that are deteriorated, outmoded, and insufficient to support modern clinical research.

Several studies conducted by NIH maintenance staff, architects, and engineers; nationally recognized architectural/engineering firms; and validated by an independent review by the U. S. Army Corps of Engineers, indicate serious and widespread deficiencies throughout the existing building. The studies concluded that immediate action is necessary to avoid widespread and potentially catastrophic failures. An interim program, the Clinical Center Essential Maintenance and Safety Program, has been initiated to restore reliability to the central mechanical system. However, this is just a stopgap measure designed to provide the Clinical Center with 12 to 15 years of continued service until this renewal program can be implemented and completed. If the Clinical Center Complex Renewal Program is delayed, the ability of the building to support modern research will be reduced. For instance, the introduction of new fume hoods is prohibited in many of the areas within the existing facility.

The renewal program will ultimately provide an upgraded Clinical Center Complex beginning with a new tower containing a new hospital and the minimum amount of laboratory space required to support the clinical research program. This will be followed by a sequential, phased renovation of the original structure to house the major portion of remaining laboratories and other functions currently within the Clinical Center. This approach is consistent with the recommendation of the NIH External Advisory Committee Report as requested by the FY 1994 House Appropriations Committee Report.

This request will provide for the design development and related construction quality management for the hospital and laboratory addition.

Consolidated Laboratory Building

FY 1996 Budget Request..$32,723,000

In 1993, the Round Robin Program was reevaluated, based on an independent study by the U. S. Army Corps of Engineers. It was determined to be inappropriate from an engineering and resource standpoint to renovate Buildings 2, 3, and 7 as laboratory facilities. To provide the necessary laboratory space lost by Buildings 2, 3, and 7, as well as to replace other existing temporary research facilities, a new facility (the Consolidated Laboratory Building) was recommended by the U. S. Army Corps of Engineers and is proposed as a continuation of the Round Robin Program. The new building would provide a total of 248,000 gsf.

To address this critical need for modern laboratory space, NIH intends to propose a reprogramming to provide funds for the design and part of the construction for the Consolidated Laboratory Building. A reprogramming letter will be submitted to the Appropriations Committee on the FY 1996 President's Budget request for NIH. The reprogramming request will include funds previously appropriated for the Nonhuman Primate Facility; the William H. Natcher Building, Phase II; and the Round Robin Program.

Funds included in the FY 1996 request will provide for the balance of funds needed to totally fund the construction of the building. Total design and construction cost is estimated at $93.123 million.

Repairs and Improvements

FY 1996 Budget Request... $19,427,000

The Repairs and Improvements (R&I) program provides for major repairs and improvements to the physical plants at Bethesda, Poolesville, Baltimore, and Frederick, Maryland; Research Triangle Park, North Carolina; Hamilton, Montana; Perrine, Florida; and other field stations for which NIH has the property-holding responsibility. The costs for some of the projects are recurring and substantial. For example, some projects such as roofs, roads, structures, building and underground utilities require ongoing repairs and maintenance to preserve or achieve reliable and safe conditions. For other projects, the costs are largely one-time, often unpredictable expenditures for major items of equipment requiring emergency repair or replacement such as transformers, chillers, and cooling towers.

In addition, this program supports adjustments to the infrastructure utility systems to provide necessary capacity to accommodate changes in the direction of research. These repairs or replacements require immediate attention, and thus are not suited to a schedule of expenditures such as found in the Infrastructure Modernization Program.

Addition to Program and Support Facilities, NIEHS

FY 1996 Budget Request.. $6,000,000

Funds are proposed to complete the construction of the laboratory addition at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. This will allow for the relocation of programs from leased facilities into one consolidated laboratory building. Design was completed in the spring of 1992. Appropriations through FY 1995 are being used for construction of the foundations and reinforced concrete shell of the four-story laboratory module; associated site work, parking, and underground utilities; partial installation of primary mechanical and electrical systems; renovation of the high bay area; and improvements to the power plant to support the new module.

The completed structure will provide a major building addition to the existing Building 101. The addition will provide 57,500 net square feet of new building space for research laboratories after completion.

Turner Construction Claims, North Carolina

FY 1996 Budget Request.. $5,400,000

The Department of Health and Human Services awarded a construction contract for the development of the National Institute of Environmental Health Sciences permanent facilities in the Research Triangle Park, North Carolina, in May 1977. During construction, a number of contractual disputes arose between the Government and Turner Construction Company. These disputes eventually developed into full litigation before the Armed Services Board of Contract Appeals ruled in favor of the contractor.

All claims against the NIEHS permanent facilities were settled in July 1991. The total claims paid by the U. S. Department of the Treasury amounted to approximately $25.4 million. The Department of the Treasury was amenable to NIH's proposal of annual installment payments of $5.0 million per year to the Treasury until the balance is paid in full. The funds included in this request will provide the final payment.

THURSDAY, MARCH 23, 1995.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, DIRECTOR
EDWARD McMANUS, DEPUTY DIRECTOR
DR. JACK McLAUGHLIN, ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH
CAROL LIPSON FIVOZINSKY, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. The subcommittee will come to order. We continue our hearings on the National Institutes of Health with the National Eye Institute. I'm delighted to welcome Dr. Carl Kupfer, the Director, who is the Dean of the Directors at NIH, having served since 1970. So we very much appreciate your coming to testify. Please introduce the people at the table, and proceed in any way you'd like.

INTRODUCTION OF WITNESSES

Dr. KUPFER. Thank you, Mr. Chairman. I would like to introduce those at the table. To my far left is Mrs. Carol Fivozinsky, who is our Budget Officer. Next to her is Mr. Edward McManus, who's the Deputy Director of the National Eye Institute. To my right is Dr. Jack McLaughlin, Associate Director of Extramural Research, and to his right is Dr. Varmus. Mr. Bill Beldon is sitting in as the representative for the Department.

OPENING STATEMENT

I'd like to summarize my statement, if I may, sir.

During the past year, we completed a very interesting clinical trial dealing with a condition that causes sudden blindness in the elderly. This condition affects about 6,000 to 7,000 people a year. Over the last four or five years, many ophthalmologists felt that the best treatment was an operation that would relieve the pressure on the optic nerve.

Because the optic nerve suddenly stops functioning, it was thought that fluid buildup around the optic nerve may be the cause and decompressing the nerve by releasing the pressure would result in improvement. It was felt that only about 10 percent of these people would improve spontaneously without any intervention.

We decided to do a clinical trial, and the community was very supportive. The results of the clinical trial were published just two months ago. They demonstrated that over 40 percent of the people will spontaneously recover vision without any intervention, and the operation not only is of no benefit, but seems to be somewhat harmful. So we have not only stopped an intervention which is not of benefit, but by doing this, there has been a major economic savings in terms of the amount of money that does not have to be spent for this intervention.

A second clinical trial which developed a very interesting outcome dealt with the condition of optic neuritis. This is an inflammation of the optic nerve, which very often is a predecessor to the development of multiple sclerosis. The results of this clinical trial showed that if a physician decides to treat it, it is better to treat it with intravenous steroids rather than oral steroids. The trial also demonstrated that those who were treated with intravenous steroids were much less prone to go on to develop multiple sclerosis. So again, here was the power of clinical trial methodology in defining what should and should not be done in terms of therapy.

A new drug has now been developed after many years of waiting for this particular development. Back in the 1950s, a class of drugs called carbonic anhydrase inhibitors was developed to reduce the production of fluid in the eye in patients with glaucoma. This had to be given systemically, by mouth, and had many side effects. In the last year, a topical preparation has been successfully produced and should be on the market by May of 1995. It's been approved by the FDA. I might say that this development, which sounds very simple, took 15 years of support from the National Eye Institute before it was turned over to commercial developers, who were able to make it into a commercially viable product.

Moving on to another important development which I think will see the light of day in another year or so, we have now been able to isolate a natural aldose reductase inhibitor. The reason an inhibitor of aldose reductase is so important is that we think that this enzyme, aldose reductase, plays a role in the causation of diabetic eye disease. If we can inhibit it safely and effectively, we can perhaps slow down or even prevent the complications of diabetic eye disease. Now that we have a natural inhibitor, we hope to bring this to a state where human trials can begin in the next year or so.

We are still working very hard on a therapy for cataract, just to slow down the development of cataract. If we can slow it down by 10 years, we'll probably reduce by about 45 percent the number of patients requiring cataract surgery. The major hypothesis now is that there is oxidative damage to the lens. This is particularly important, because it is thought that oxidative damage may be the basis for many systemic degenerative diseases. If we can learn how to turn off this damage in the lens, it may have very far-reaching implications for other diseases.

In the coming year, we want to stress continued support of basic fundamental research, and we hope that this research will eventually result in clinical applications in the following areas. We're very much involved in the genetic and nutritional factors involved in development of cataract, glaucoma, retinal degeneration such as retinitis pigmentosa, and macular degeneration.

The National Eye Institute is a participant in the NIH Brain and Brain Disorders initiative, and therefore we will continue investigations in the regeneration and adaptability of the visual system, and the molecular mechanisms of myopia, that's nearsightedness. And

I think we've suddenly become very much involved in new approaches to this condition, research on the control of eye movements, which will have an impact on strabismus, and development of aids for individuals who are visually impaired or blind.

And finally, I'd like to make a comment about an area which just came to my attention. Much of the research supported by the National Eye Institute over the past 25 years has contributed to the United States' commercial and industrial activity. To try to document that, we went to an organization that reviewed patents from 1975 to 1993. During this time, there were 8,000 patents dealing with products and technology related to vision, magnifying glasses and a whole range of medical and surgical technologies dealing with the visual system.

For those 8,000, approximately 50 percent of the cited publications had referred to research supported by the National Institutes of Health. And of those publications, half of them, 50 percent, attributed research support to the National Eye Institute. Now, we are going to continue to look at this, and determine what the impact was in terms of which companies profited from the research done by the National Eye Institute.

In conclusion, Mr. Chairman, the fiscal 1996 budget request for the National Eye Institute is $300,693,000. I'd be happy to answer any questions.

[The prepared statement and biography of Dr. Carl Kupfer follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Eye Institute

Mr. Chairman, I am pleased to provide an overview of the NEI's recent advances and to describe several of the important research challenges that we are positioned to meet in the upcoming year. In my presentation, I will highlight examples of how NEI research helps to make America a leader in the development of new technologies and products for the treatment and prevention of eye disease.

In 1994, a clinical trial conducted by the NEI intramural research program showed that a new drug-releasing device was effective in treating cytomegalovirus (CMV) retinitis, a sight-threatening disease that affects one in four people with AIDS. The tiny device is surgically placed into the eye where it releases the anti-viral drug ganciclovir over a period of several months. Ganciclovir has proved effective in controlling the progression of CMV retinitis, but it currently must be administered through daily intravenous treatments. Because people with AIDS are never cured of CMV retinitis, they must undergo this form of therapy each day for the rest of their lives. In contrast to the costly, daily intravenous treatments, which significantly diminish the patient's quality of life, the ganciclovir implant takes less than one hour to insert under local anesthesia, and has been shown to eliminate all signs of active infection with CMV for approximately 8 months, at which time it can be replaced. It also significantly reduces the cost of treating CMV retinitis.

Because the U.S. population age 65 and older is expected to double by the year 2030, the eye diseases associated with aging are a focus of NEI research. By the year 2030, more than 66 million Americans will be at risk for these common eye diseases. Maintaining vision as we age helps older people maintain a high quality of life, remain self-reliant, and live at home.

The most common form of cataract is related to aging. Approximately 8.5 million Americans are affected by this condition, a clouding of the eye's lens that can cause vision loss. Approximately 1.5 million cataract surgeries are performed each year at a total cost of $5 billion. Reimbursement for cataract surgery accounted for 12 percent of the Medicare Part B budget at the turn of the decade. If the rate of cataract development could be slowed by just 10 years, the need for surgery would be decreased by almost half. In 1995, this means a potential annual savings of $2.5 billion in health care costs. Toward this end, NEI intramural investigators and grantees are searching for the cause of cataracts and ways to slow or prevent their progression. NEI will continue to support studies aimed at counteracting the oxidative damage thought to be an important factor in cataract development. In addition, NEI supported much of the research that underpinned development of the intraocular lens that almost all people who undergo cataract surgery have inserted as a replacement after their own lens is removed; eighty percent of these lenses are produced by American manufacturers.

Glaucoma, which is often associated with an increase in intraocular pressure, is another potentially blinding disease that is expected to increase as the population ages, and is estimated to affect approximately 3 million Americans. A disproportionate number of those affected are African Americans, and glaucoma is the leading cause of blindness among this population. NEI-supported basic research has yielded products useful in diagnosing and treating this disease. For example, an NEI grantee has discovered a topical carbonic anhydrase inhibitor that effectively lowers pressure in the eye and has few side effects. The FDA recently approved the drug for marketing. NEI-supported scientists have also shown that prostaglandins, another class of drugs, lower pressure in the eye. However, problems with side effects have kept them from being developed for therapeutic purposes. The recent discovery that a form of prostaglandin is effective and safe has now opened the possibility of another promising new drug.

Another visual problem affecting as many as 6,000 older individuals annually is non-arteritic ischemic optic neuropathy. This condition, thought to be caused by reduced blood flow to the optic nerve head, is thought to be the most common cause of sudden visual loss in older Americans. It had been treated by optic nerve decompression surgery with careful follow up, or by careful follow up alone. To compare these two management strategies, NEI conducted the Ischemic Optic Neuropathy Decompression Trial (IONDT). The trial recently concluded that the decompression surgery, a difficult and expensive procedure, is no better than careful follow up alone, and may even be harmful. A clinical alert was distributed to ophthalmologists and neurologists nationwide to inform them of this important finding. Estimates of the annual potential cost savings that the nation will realize by not performing this operation range between $30 and $60 million.

The ten-year follow-up results from NEI's Prospective Evaluation of Radial Keratotomy or PERK Study were released in 1994 and also received wide publicity. PERK is the first large clinical study to evaluate the long-term effects of a controversial procedure called radial keratotomy (RK) used to correct nearsightedness. About 250,000 of these procedures are performed annually, a significant increase from the 30,000 operations performed just five years ago. Data from the PERK study suggest that although RK is a reasonably safe and effective technique, it can produce instability in vision that may last up to 10 years after surgery. This may cause some individuals who have RK to need reading glasses at an earlier age than if they had not had the surgery. NEI made this important finding known to the medical community and released information to the public through the media resulting in reports in more than 250 newspapers around the world, including the front page of *USA Today*, reaching more than 25 million people.

The PERK and the IONDT are but two examples of how NEI conducts and sponsors research that has a direct effect on patient care and highlights the importance of informing the public of findings that may affect their treatment options. Seventeen NEI-sponsored clinical trials conducted in the last five years have reported results that were effectively disseminated to the medical community and the public. In addition to publicizing important research findings, NEI also makes eye health information available to the general public to help Americans protect their vision.

Diabetic retinopathy is the leading cause of blindness among working-aged Americans. NEI investigators recently discovered growth factors that may play an important role in the development of abnormal and destructive blood vessels in diabetic retinopathy, opening the exciting possibility that suitable inhibitors of the process can be found. NEI investigators have found that in animal models, blocking the enzyme aldose reductase prevents diabetic retinopathy. They have also developed an extremely potent aldose reductase inhibitor and are investigating its potential as an effective treatment for the disease.

NEI began studying the use of laser surgery as a treatment for diabetic retinopathy in the 1970's. According to NEI epidemiological and economic analyses, this treatment now produces societal savings of between $1.2 and $1.6 billion annually, primarily in reductions in lost productivity due to blindness. Lasers are now used to diagnose and treat a full range of eye conditions including retinal detachments, glaucoma, and the most severe form of age-related macular degeneration, an eye disease that affects millions of older Americans. The results of NEI-supported research, including innovative projects supported by the Small Business Innovation Research grants program, have stimulated private sector development of new laser technologies. America's thriving laser industry produces 80 percent of the laser-based ophthalmic devices used to diagnose and treat patients throughout the world.

NEI-supported vision research also has an impact on related medical disciplines. For example, scientists have made an important discovery concerning optic neuritis, an inflammation of the optic nerve that strikes more than 25,000 Americans yearly, primarily women between the ages of 18 and 45. At least half of the people with first-time optic neuritis will eventually develop multiple sclerosis, a progressive neurological disease. NEI-supported scientists found that treating these optic neuritis patients with a combination of intravenous and oral corticosteroids significantly lowers their risk of developing multiple sclerosis.

Although we have made much progress in many areas, this progress must be continued. The following are some examples of the many research opportunities that will be pursued in fiscal year 1996. NEI will continue to pursue research into the leading causes of visual impairment for older Americans. These include age-related macular degeneration, cataract, diabetic retinopathy, and glaucoma. Age-related macular degeneration is one disease for which the identification of genetic, nutritional, and other age-related changes in the retina will be studied. In one of its future research efforts on cataracts, NEI will study how to augment the lens's natural defense mechanisms in order to prevent or retard cataract formation. Future investigation concerning diabetic retinopathy will include the development of new drugs and molecular genetic techniques to inhibit aldose reductase activity, as previous studies have demonstrated that this enzyme is involved in the pathogenesis of the disease. Future research on glaucoma includes characterization of the glaucoma "gene;" research to determine why the rate of glaucoma is higher and the disease possibly more severe in African Americans; and the development of new drugs and biologics to control pressure in the eye.

As an important component of the NIH Brain and Brain Disorders Initiative, NEI will pursue investigations on visual system development, visual system regeneration following injury, molecular mechanisms that cause myopia, control of eye movement, and development of advanced aids for individuals who are visually disabled or blind.

Gene therapy is also an area of research that will be emphasized in the upcoming fiscal year. The molecular mechanisms by which known gene defects in various forms of retinitis pigmentosa produce the disease will be studied. We also are at work on the development of gene therapy approaches to treat the disease. This promising new area of research may be a major hope for the treatment of several of the diseases that cause vision loss.

The NEI conducts or supports more than 80 percent of the important basic or fundamental research on the human visual system in health and disease. Investment in this research provides practitioners with improved strategies for patient care. It provides the public with information they can use to protect their vision. It also provides discoveries that are the basis for private sector development of new drugs and technologies.

Mr. Chairman, the FY 1996 budget request for the National Eye Institute is $300,693,000. I will gladly answer any questions.

CARL KUPFER, M.D., Director, National Eye Institute
February 9, 1928. New York, New York.

Education: A.B., Yale Univ., 1945-48. M.D., The Johns Hopkins Medical School, 1952 Certified. American Board of Ophthalmology, 1958.

Professional History: Internship and Assistant Residency, Wilmer Eye Inst., Johns Hopkins (JH) Hospital, 1952-54. Lab. Asst., Biostat., JH School of Medicine, 1953-58. Research Fellow in Ophth., Harvard Medical School, 1958-60. Instructor in Ophthalmology, Harvard Medical School, 1960-62. Assistant Professor of Ophthalmology, Harvard Medical School, 1962-66. Prof. and Chairman in Ophth., Univ. of Washington School of Medicine; Research Affiliate, Univ. of Washington Primate Ctr., 1966-70. Director, National Eye Institute, 1970-present. Acting Deputy Director for Intramural Research, NIH, 1991-1992.

Professional Organizations: Am. Physiological Society; Assoc. for Research in Vision and Ophth.; Am. Academy of Ophthalmology; Am. Ophthalmological Society; Pan Am. Ophth. Society; Johns Hopkins Univ. Soc. of Scholars; Member, Inst. of Medicine, National Academy of Sciences.

Honors and Awards: The Secretary's Special Citation, DHEW, 1972; The Superior Service Award, DHEW, 1974; Presidential Rank Award of Meritorious Executives, 1983; Migel Medal, Amer. Foundation for the Blind, 1976; Public Service Award in Ophth., Amer. Academy of Ophth. and Otolaryngology, 1977; Special Award of Honor, The Assn. for Research in Vision and Ophthalmology (ARVO), 1983; David Rumbough Memorial Scientific Award, JDF, 1983; The Lighthouse Pisart Vision Award, 1984; Cavera Medal of Univ. of Rome, 1985; The Mildred Weisenfeld Award for Excellence in Ophth. 1987; Presidential Distinguised Rank Award, 1991; Statesmenship Award, Joint Commission on Allied Health Personnel in Ophthalmology, 1991; Lions Clubs Intl. Humanitarian Award, 1992; Kupfer Award of the ARVO, 1993; Leadership Award, AOS, 1993; Benjamin F. Boyd Humanitarian Award of the Pan-Am. Assn. of Ophthalmology, 1993; Joslin Diabetes Center-MediSense Award, 1994; RP Foundation Humanitarian Award, 1994; Gold Jose Rizal Medal, 1995.

Other Scientific Activities: Editorial Board, Investigative Ophth., 1969-1977; Editorial Board, Am. Journal of Ophth., 1971-1983; Member, Scientific Advisory Committee, Fight for Sight, 1971-present; Member, National Diabetes Advisory Board, 1976-present; Member, Board of Directors, American Diabetes Association, 1994-present.

International Appointments: Member, Board of Trustees, HKI, Inc., 1975-present; Member, Intl. Vitamin A Consultative Group, WHO, 1973-present; Member, WHO Advisory Group for Prevention of Blindness Prog., 1978-1984; Consultant, Pan Am. Health Organization, 1978-present; Coordinator for USA, Priority Area "Eye Diseases," U.S.-U.S.S.R. Prog. for Health Cooperation, 1978-present; Member, WHO Expert Advisory Panel on Trachoma and Prevention of Blindness, 1979-present; Dir., WHO Collaborating Ctr. for the Prevention of Blindness, National Eye Inst., Bethesda, MD, 1979-present; Pres., Intl. Agency for the Prevention of Blindness, October 1982-1990. Consultant in India for the World Bank, 1992-present.

25TH ANNIVERSARY

Mr. PORTER. Dr. Kupfer, do you have a date on which you'll be celebrating your 25th anniversary?

Dr. KUPFER. It's this year, sir.

Mr. PORTER. But is there a particular date?

Dr. KUPFER. Yes, January 1st to December 31st.

Mr. PORTER. Oh, yes. [Laughter.]

Well, when I said you were the Dean of the Directors, I meant that as a statement of profound respect. This is a Republican that doesn't believe in term limits. I think experience counts, and I think it's wonderful that you have provided the leadership at the National Eye Institute for the last 25 years. Obviously, you've done a wonderful job, and we very much appreciate your work.

Dr. KUPFER. Thank you, sir.

RETINOPATHY OF PREMATURITY

Mr. PORTER. You talked about diabetic retinopathy, and said that it would be a year or so before your researchers would begin to test this work on human beings. In the January issue of Science magazine, this research was described, and it indicated it would also help prevent blindness in premature infants. How common a risk is blindness in premature babies?

Dr. KUPFER. Well, sir, that's a very good question. As you may recall, in the 1950s retinopathy of prematurity was quite common. In fact, 20 percent of all premature infants born became blind. It was really an epidemic. And research supported by the NIH at that time showed clearly that it was high levels of oxygen that caused the blindness. As soon as the amount of oxygen administered to these infants was decreased, the incidence dropped from 20 percent to less than 1 percent.

However, as time went on, the ability to save smaller and smaller premature babies improved. Now we are saving premature babies that weigh less than 1,000 grams, which is a fraction of the normal weight at birth. As a result, just to keep them alive, there was the need to again increase the amount of oxygen, which can produce devastating changes in the eye. About 600 to 700 of these premature infants that are kept alive become blind each year.

We concluded a trial about three years ago in which the use of cryotherapy—freezing that part of the eye that is growing new vessels and shouldn't be growing new vessels—prevented blindness by about 50 percent. But there still is a significant number of prematures who go blind.

RADIAL KERATOTOMY

Mr. PORTER. You indicate that the surgical procedure, RK, radial keratotomy, is generally safe, but not without its problems. The procedure seems to be commercially marketed quite heavily, particularly on the radio. On the basis of the clinical trial you conducted, would you say that the public to which this is being marketed is likely to benefit from the surgery?

Dr. KUPFER. This is an interesting trial, inasmuch as it began some 11 or 12 years ago at the instigation of the ophthalmologic community. They were concerned with the delivery of radial keratotomy to large numbers of people who wanted to get rid of their glasses and have this surgical procedure. Our main concern was to be sure that it was not only effective in correcting myopia, but was also safe. As a result, we designed this trial so that we would have 10 years of follow-up, which is a very long time for follow-up in clinical trials.

We can now say it is safe, in terms of major complications, although we have to keep in mind that 10 years may not be long enough to detect all the late changes. In terms of effectiveness for low levels of myopia, it probably is fairly effective. The problem is, that with time, a number of these people who were perfectly corrected for the first two or three or four years begin to become farsighted.

This causes two problems. The first is that instead of needing to wear reading glasses when they are 45 or 50, they may need to wear them when they're 35 or 38. Once again, they are confronted with the need to wear glasses. Second, as they become more farsighted, they have to wear glasses to see in the distance. As long as the individual is aware of these limitations, I think personal preference is going to dictate whether they will go ahead and have the surgery or not. Our responsibility was to make them as well informed about the limitations as possible.

APPROVAL OF SURGICAL PROCEDURES

Mr. PORTER. When you have a new or newly used surgical procedure like this, is there a body that has to approve this, like FDA has to approve a new drug, or can practitioners simply go ahead and use this procedure?

Dr. KUPFER. A new surgical procedure need not be approved. A new device has to be approved by FDA. For instance, if a laser is developed to treat a condition, FDA will be involved in approving the device. But a new surgical procedure usually does not require FDA approval. However, we do want to protect the American public, and as a result, we will very often subject new surgical procedures to this sort of clinical trial.

Mr. PORTER. But the clinical trial takes some time, and meanwhile the procedures can go forward. Even if they are harmful, they can go forward.

Dr. KUPFER. Well, we hope that during the course of the clinical trial there will be a reluctance on the part of the medical community to widely use this procedure. For example, in the case of the surgery for decompression of the optic nerve, once it was known that we were doing a clinical trial, the number of procedures probably decreased. And now that we know that it is of no benefit, there will be very few surgeons who perform this procedure.

INFORMATION DISSEMINATION

Mr. PORTER. Now, that brings me to the next question. You seem to be very successful at getting broad media coverage of your research findings. How do you go about doing that?

Dr. KUPFER. We have a very active public information office, and we feel strongly that the results of clinical trials should be disseminated to the public and to the ophthalmologic profession and the optometric profession—those who are taking care of the eye health needs of the American people.

Mr. PORTER. When you say public affairs office, is it the Eye Institute?

Dr. KUPFER. Yes, sir.

Mr. PORTER. It's your own, not NIH's?

Dr. KUPFER. Right. We do keep in mind that most of these clinical trials are multi-center trials, with 10 to 20 clinics cooperating. Once the results are in and the conclusions are clear and have been approved by the data and safety monitoring committee, the group that oversees the trial, we feel we have an obligation to let the patients know, to let the practitioners know, and to let the public know. We have an orderly procedure for releasing this information, and this is what we've followed.

GENE THERAPY

Mr. PORTER. Your justification describes a virus that is being tested to deliver genes into the cells of the retina. What sort of diseases is this form of gene therapy likely to be used for, and is the eye a less complex target for gene therapy than other bodily organs?

Dr. KUPFER. The conditions that we would be interested in would be conditions that cause various retinal degenerations; retinitis pigmentosa is a particularly good example. Some forms of genetic macular disease in young people would be another possibility.

I don't think the retina is an easier or more difficult target than other tissues for the delivery of a gene. But I think we are in a very good position to test whether the introduction of the gene has accomplished the results we're looking for. Not only can we see the retina on direct examination, but we can also measure its function in a much more precise way than perhaps any other organ system in the body.

So in terms of knowing whether we've been successful or not, we're in a very good position. In terms of delivering the virus, we have all the problems of getting the right combination of events that would be true for any other organ, except a tissue in which you could deliver the virus topically, such as the bronchus or perhaps the cornea. There the delivery would be much simpler.

Mr. PORTER. This may not be a proper question, but is there any way to tell how far we are away from treating retinitis pigmentosa in the way you described?

Dr. KUPFER. There are a number of major hurdles, and I would be a little reluctant to give a specific timetable. There is a variant to retinitis pigmentosa called gyrate atrophy, and we're within two to five years of delivering genes in that condition, to see if it will be successful. But that is a very rare condition, and it will serve perhaps as a model for us to learn how we can approach retinitis pigmentosa.

Mr. PORTER. Thank you.

Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Kupfer, it's a pleasure to see you again before our subcommittee.

Dr. KUPFER. Thank you, sir.

NATIONAL DIABETES MONTH

Mr. STOKES. Let me start by taking time to congratulate you and the Institute upon the celebration of its 25th anniversary. It's nice to know that you're having that type of celebration.

Doctor, let me start with asking you a question about the National Diabetes Month featuring the importance of diabetics receiving a dilated eye exam. What is the extent of the ocular complications of diabetes in the American population in general, and also in minorities?

Dr. KUPFER. We were very fortunate in the recent National Diabetes Month, which was, in November of 1994 to have the American Diabetes Association, the Juvenile Diabetes Foundation, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Eye Institute all cooperate in focusing on the treatment of diabetic eye disease. This treatment has been well-substantiated and can reduce blindness by more than 95 percent in diabetics. One of the major problems was to deliver this message to the public.

The dilated eye examination allows the examining eye-care practitioner to determine whether diabetes has affected the eye to the point where treatment is indicated, the treatment being laser treatment. And therefore, the only way to really make this determination is to make the pupil very large, so one can look in and determine what is going on, and whether this individual requires treatment.

In addition to the diabetes organizations, we had the cooperation of the American Academy of Ophthalmology and the American Optometric Association. There were a series of radio programs, news releases, and many of these were targeted to African Americans. As you were aware, sir, in the National Eye Health Education Program, we have identified two diseases, glaucoma and diabetes, both of which are very prevalent in African American populations. So we made a specific effort to target this population in our public information releases.

The effort in one month cannot be the only effort made. There's got to be a continuing program to remind the American public of the need for having a dilated eye examination, and therefore, the NEHEP program is doing this, not only for African Americans, but also for other affected minorities.

NEUROLOGICAL RESEARCH

Mr. STOKES. Doctor, we've recently had some excellent testimony here before our subcommittee from a group of Nobel laureates. They stressed to us the importance of neurological research as being one of the most important areas that if enhanced, offered considerable opportunity to further medical advances. In testimony before this subcommittee over the years, you've often referred to the eye as being the window to the brain. Tell us what makes this area of research a prime investment for your Institute at this time.

Dr. KUPFER. The eye and more specifically the retina are actually a part of the brain and central nervous system. It's the only part of the brain and central nervous system that we can observe directly. We can see the optic nerve, which is also part of the central nervous system, and the blood vessels to the retina. Many of the diseases that occur in the retina also have an ancillary finding in the brain, so that in the first instance, the eye care professional looking at the retina, looking at the optic nerve, can interpret what might be going on in the brain.

Many of the strategies, in terms of understanding the disease processes in the retina, and its treatment, will be generalizable also to the brain. For instance, gene therapy for retinal disease will have applications to gene therapy for diseases in the brain. The ability to understand regeneration in the retina, and in the optic nerve, will have application to the brain. The opportunity to understand the adaptability of how retinal tissues can take on new tasks when other retinal tissues are damaged, that's something we want to do in the retina. It will have applicability to the brain. So in a sense, much of the research that is going on in the retina will be generalizable to the brain.

The retina is a particularly nice structure also because it is laminated. It is layer after layer, and therefore one can dissect the different functional areas of the retina very, very carefully and very well, which is a little more difficult to do in the brain. There are many aspects of neuroscience research where we in the National Eye Institute and our colleagues in the National Institute of Neurologic Diseases and Stroke interact intimately. I know the next person who will be testifying will be the new Director of the Neurology Institute, and he and I have been talking about our collaborative activities.

DECADE OF THE BRAIN

Mr. STOKES. For a number of years, a gentleman who served on this committee and a much revered Member of this committee, now deceased, Sil Conte of Massachusetts, promoted an initiative called Decade of the Brain.

Dr. KUPFER. Yes, sir.

Mr. STOKES. Is that still a viable initiative?

Dr. KUPFER. Well, I certainly hope so, and I do think so. A number of Institute Directors at NIH under the leadership of Dr. Zach Hall, the new Director of the Neurology Institute, have met and have recognized the critical need to support the Decade of the Brain initiative. In fact, the opportunities are so great that we would be remiss if we do not do this. We now have what is called the NIH Brain and Brain Disorders initiative. I'm happy to say that Dr. Varmus is very supportive of this, and I think we will be moving ahead very rapidly in the next few years making this a viable initiative in the remaining portion of the last decade of the 20th century.

STROKE RESEARCH

Mr. STOKES. Doctor, stroke continues to be the third leading cause of death in the United States. Is the Eye Institute involved in stroke research, and if so, to what degree are you focusing on the health problem?

Dr. KUPFER. We are involved in the sense that stroke represents an occlusion of a vessel, with its attendant destruction of tissue that ordinarily would be supplied with blood by this vessel. And we have the same activity occurring in the retina. The retina is supplied by a central retinal vein and a central retinal artery. In each case, either the vein or the artery can be occluded. The damage to the retina is quite similar, in fact, almost identical, with the damage to the brain. We are trying very hard to understand what causes the damage and to learn how to prevent it. Once again, if we found out how this worked, it would be applicable to the brain and vice versa.

ADMINISTRATIVE SUPPLEMENTS

Mr. STOKES. Dr. Kupfer, at last year's hearing, we discussed the NEI's use of administrative supplements to research grants for the support of underrepresented minority scientists and students. At that time, you indicated that you were expecting to increase your participation in this program. Can you tell us to what extent this has occurred?

Dr. KUPFER. Yes, sir. In fiscal year 1993, we awarded 27 supplements, costing about $819,000. During 1994, we awarded 37 supplements, totalling about $983,000. The number of awards made to African Americans increased from 14 to 21. This is a very high priority in our Institute, and we are looking, continually for opportunities to increase this number.

CATARACT

Mr. STOKES. According to your Congressional justification, you tell us that more than 1.5 million cataract surgical procedures are performed each year at a cost of more than $5 billion. Tell us, how does this number of surgical procedures compare with that for other diseases and disorders?

Dr. KUPFER. Cataract surgery is probably one of the most common procedures performed. As far as Medicare is concerned, it accounts for about 12 percent of Medicare Part B. So it does represent a major commitment upon the part of Medicare funding. I'm not sure I would say it is the most commonly performed, but certainly one of the most commonly performed.

Mr. STOKES. Are you also doing clinical trials in this area?

Dr. KUPFER. Yes, sir, we have a clinical trial called the Age Related Eye Diseases Study in which we are looking at both cataract and macular degeneration and trying to slow their progression by using antioxidants. I had mentioned earlier that we think that oxidative damage is one of the major mechanisms for the production of cataract, or opacification of the lens, and it probably plays a role in many other degenerative changes.

We are conducting a clinical trial, recruiting 4,600 patients across the United States in 10 clinics. The recruitment will probably be completed this May, and then we will have a five-year follow-up. We are using nutritional supplements to determine whether they will be of benefit in slowing down the cause of cataract.

Mr. STOKES. Thank you, Dr. Kupfer.

Thank you, Mr. Chairman.

Mr. PORTER. Dr. Kupfer, can you tell us how oxidative damage occurs, what's the mechanism?

Dr. KUPFER. Yes, sir, I certainly can. Perhaps I could just confine my remarks to the lens, because I think it's easiest to see. The lens basically consists of two portions. The lens is like the skin, it continually grows throughout life. But unlike the skin, it doesn't keep shedding, since it's within the eye. And therefore, it keeps compressing the oldest fibers into its interior. So at the very, very center of the lens are the fibers that were laid down when the fetus was formed. And then there's the embryonic lens, the juvenile lens, and finally the lens fibers that are being laid down today and tomorrow and the next day.

Therefore, we can divide the lens into a nucleus, which is the old fibers, and the cortex, which is the newer fibers. Now, the thing about the nucleus that is very important is that as these fibers become compressed, they lose their capability of having enzymes, of having DNA, and of having most of the usual constituents of normal cells. But they do have the proteins that make up the cells.

These proteins have portions that have an affinity for one another, what we call linkage. As these proteins begin to link together because of the oxidation that is taking place, they form larger and larger aggregates. When the aggregate becomes so large that the space between them is smaller than the wave length of light, then light cannot pass through. And that is thought to be the cause of what we call the nuclear cataract, this oxidative damage causing more and more aggregation.

Now, in the case of the cortex, probably oxidative damage occurs to the cell membrane, which causes leakiness, water comes in, the cells swell and eventually die. So those are two of probably many oxidative damage pathways that can occur.

CLINICAL TRIALS

Mr. PORTER. Dr. Kupfer, you had a host of clinical trials come on line or be completed recently. Does this reflect the maturity of vision research that many basic research ideas have been developed into clinical findings that are now ready for broader testing?

Dr. KUPFER. Yes, sir, about 10 percent of our budget is devoted to clinical trial support, and that probably represents the right balance between basic laboratory fundamental research, which will eventually result in a finding that can be applied clinically. We have conducted in excess of 25 clinical trials during our last 25 years.

I think there are still many more clinical trials to do. I take great pride that the opthalmalogic community has really become very knowledgeable in the conduct of clinical trials. I think we've been very successful in bringing to the American public well-proven therapies.

Mr. PORTER. How many will you support in 1996?

Dr. KUPFER. I would say approximately 23. And I can check that for the record, sir.

[CLERK'S NOTE.—Subsequent to the hearing, the number of clinical trials was corrected to 14.]

LASERS

Mr. PORTER. Your testimony describes the use of lasers. Will the laser eventually replace other forms of eye surgery? My impression is that laser surgery is less expensive, less invasive, and less prone to complications than other surgery. Is that correct?

Dr. KUPFER. I think that's a very good assessment. Lasers have been clearly demonstrated to be of great benefit in the treatment of diabetic retinopathy. It is being used very extensively in the treatment of glaucoma. We've just completed a trial in which laser therapy as an initial treatment was compared to medical therapy, which is the standard traditional treatment. The results were that laser therapy had comparably good results to the medical therapy. So now we have two possibilities for patients developing glaucoma.

Lasers are now even being developed for the treatment of cataract. How this is going to turn out, I don't know. But the idea is to make a small opening in the capsule of the cataract and have the cataractous material slowly absorbed, leaving a clear space that would then enable one to put in some sort of artificial lens.

I think we're just beginning to see the utilization of laser technology, not only in terms of treatment, but in terms of diagnosis. The diagnostic applications are just beginning.

STRABISMUS

Mr. PORTER. Your justification also describes surgery for strabismus as one of the most common surgeries of this kind. Does the use of lasers have potential in that kind of surgery?

Dr. KUPFER. Sir, I don't think the laser has immediate application for strabismus. Our research in strabismus has really focused on improving the predictability of our surgery on the eye muscles to straighten the eyes. We did do a clinical trial to show that if we were to test the child before surgery, with a prism, and determine how well the prism would correct the strabismus, our predictability of the surgery was much improved.

CONTACT LENSES

Mr. PORTER. Your research has raised questions about the safety of contact lenses, both in those who've worn them for many years and those who now use extended wear lenses. Can you tell us more about that?

Dr. KUPFER. One of the potential problems with contact lenses is in using what are called extended wear lenses. In general, the expectation is that one places the lenses in the eyes, keeps them in for seven days and seven nights, and then replaces them with a new lens.

Under the ideal circumstances this works perfectly well. But if something gets into the eye that causes a scratch on the cornea, and if there is infectious material around, and very often there is, a corneal ulcer can easily develop. And that is the major problem with extended wear contact lenses. If we could develop a lens which is completely permeable to oxygen, which the cornea needs to stay normal, then perhaps we can avoid this corneal abrasion, resulting from some trauma, and keep an ulcer from forming.

So the hope is that technology will develop a contact lens that is completely permeable to oxygen. I think that is the direction that the industry is going and that our research is taking us.

Mr. PORTER. Regular contact lenses, soft lenses, have not proven to be a problem, have they?

Dr. KUPFER. No, sir, as long as the precautions are taken to sterilize the lenses. They seem much safer than the lenses that are kept in for long periods of time.

Mr. PORTER. Does the eye have in the tear some of the same kinds of defenses as saliva has in the mouth to fight infection?

Dr. KUPFER. Yes, sir, it does.

LOW VISION AIDS

Mr. PORTER. How much of your research portfolio is devoted to the needs of those who are already blind?

Dr. KUPFER. By that, I would assume that you mean rehabilitation, low vision aids, that sort of thing. I would say probably between $3,000,000 and $4,000,000 which is about 1 to 2 percent of our budget.

Mr. PORTER. Mr. Stokes.

DISSEMINATION OF CLINICAL TRIAL RESULTS

Mr. STOKES. Thank you, Mr. Chairman, I have a couple of other questions.

Doctor, you've talked to us a great deal about clinical trials. Are we getting any better at being able to disseminate the results of those clinical trials?

Dr. KUPFER. Mr. Stokes, if I had to state right now the greatest challenge we have, it would be the dissemination of the results of clinical trials. Let me just give you one example. We have a treatment for diabetic eye disease that will reduce blindness by more than 95 percent, yet we know only half the diabetics who are at high risk for going blind, are receiving the treatment.

We are trying very hard, through focus groups, through our National Eye Health Education Program, through research, to try to find out what is the difference in behavior between those who take advantage of treatment and those who do not, to bring that treatment to all the diabetics at high risk. This is a major problem.

Mr. STOKES. So in effect, we really do not have a real good system in terms of being able to disseminate this information?

Dr. KUPFER. We can disseminate it. But I think the American public is bombarded with so much information, so much data, that it is difficult to call their attention to this particular area. We are doing research on this and trying to develop much better ways to do it. We have many partners working with us, including the American Diabetes Association, the Juvenile Diabetes Foundation, and many non–Government organizations that are also very interested in this. The American Academy of Ophthalmology has its own program to try to bring this knowledge to the general practitioners and to the patients. So it's a broad ranging approach, but I hope at one of these hearings I can say to you, we've really improved the American public's response to these dissemination efforts.

EYE MOVEMENT DISORDERS

Mr. STOKES. You may have to try T.V., you know, more American people watch T.V., but they don't do enough reading, unfortunately.

Eye movement disorders are a common symptom of neurological disease and one of the major causes of loss of vision. What research is now underway and on the horizon that could lead to a treatment for these conditions?

Dr. KUPFER. We have probably the most extensive group of researchers working on eye movements. There are two types of eye movements. There's the smooth pursuit movements that we use to track an object that is moving across our field of vision. And then there's the quick, jumping eye movements, the so-called saccadic eye movements that we use when we are reading and jump from word to word.

An understanding of how those two systems work is being very rapidly attained. As soon as we have a better understanding of the control of those eye movements, therapeutic interventions for specific diseases could result. So I think we still are in the midst of very basic research on this. We're doing our work within the brain, within the visual system that controls eye movements.

AIDS RESEARCH

Mr. STOKES. Doctor, what is the most significant AIDS research that's underway at your Institute?

Dr. KUPFER. The most recently concluded clinical trial involved treatment of an opportunistic infection associated with AIDS that affects the retina, cytomegalovirus retinitis or CMV retinitis, by placing an ocular implant inside the eye. The implant actually prevented the disease from progressing for about eight months.

There are two reasons why this was so very important. The first is that this is the first intervention for CMV retinitis that did not require daily intravenous administration of a drug. So in terms of improvement in quality of life, this was a major step forward. I think the second reason is that it opened up the entire field of the delivery of drugs inside the eye by having a tiny insert that contains the drug and slowly releases it after being placed within the eye. So the treatment of inflammatory disease, the treatment of tumors, the treatment of other conditions, is now being opened up.

MINORITY HEALTH

Mr. STOKES. Doctor, over the years, you and I have had a great deal of discussion with reference to some of the initiatives and programs related to treating the serious disparity between minority and majority health. And you've had a number of initiatives out there. Can you tell us about any progress that we're making?

Dr. KUPFER. Well, I think that one of the major problems with African American eye health is that of glaucoma, as you know. We now have two very important clinical trials ongoing in which we have made every effort, and a successful effort, to have adequate numbers of African Americans included.

The first has to do with the question: if the pressure in the eye is elevated and there is no evidence of glaucoma, can we prevent that individual from developing glaucoma if we start treating the elevated pressure? That is an ongoing study in a number of clinics, and there are significant numbers of African Americans participating in the study.

The second study is equally important. If you have a newly diagnosed glaucoma patient, should you continue to treat that patient with drops—a medical treatment which the patients do not like, because it impinges on their quality of life—or should you do immediate surgery? Immediate surgery carries with it a certain difficulty, because when one does surgery, there may be complications. But one of the end points that we're using in this, Mr. Stokes, is the quality of life issue. Patients may prefer to take the small risk and have immediate surgery and not worry about drops rather than to continue to take drops for the rest of their life.

So I think these two studies are going to have important implications for African Americans. And of course, the National Eye Health Education Program is geared specifically to Blacks over the age of 40 for glaucoma, and all diabetics, and Blacks are disproportionately represented in that group with diabetes.

Mr. STOKES. Thank you very much, Dr. Kupfer.

Dr. KUPFER. Thank you, Mr. Stokes.

TREATMENT OF EYE DISEASE

Mr. BONILLA [presiding]. There's a vote on.

Doctor, I'd like to start out by asking about any research that NEI has done that has changed the treatment of eye disease? Can you tell me about that?

Dr. KUPFER. I think there are a number of clinical trials that have been done over the past 25 years that have significantly changed the treatment of eye disease. Historically, of course, going back even further than 25 years, going back into the late 1950s, the removal of high levels of oxygen in premature infants dropped the amount of retrolental fibroplasia or retinopathy of prematurity from 20 percent blindness amongst prematures to less than 1 percent.

During the 1970s, we began the use of laser therapy in diabetic eye disease. And now we know that if a diabetic with high risk characteristics follows all the recommendations of those clinical trials, their chances of going blind are less than 2 percent. It's very, very small.

Unfortunately, many of the people with diabetic eye disease at high risk for blindness, do not seek this help. And one of the questions we've been discussing is how to get that message to be understood by the public. We're getting the message out, but it's not reaching the diabetic community, and they're not translating this into coming in for eye examinations.

We have had a major impact on patients with an inflammation of the optic nerve called optic neuritis. And this very often is a precursor of the development of multiple sclerosis. The treatment has always been oral steroids. We now find out that not only is oral steroid treatment not of any benefit, but it actually predisposes to more recurrences.

In our clinical trial, we had one group of patients randomized to intravenous steroids. That group not only recovered their vision more rapidly, but what was even more significant, fewer of them went on to develop multiple sclerosis. So I think this is a very major change in the way treatment is delivered.

With the improvement of keeping very small premature infants alive, we're now again seeing blindness from retinopathy of prematurity. We concluded a clinical trial several years ago in which freezing a part of the retina where the new vessels were growing inappropriately reduced blindness by about 50 percent. So we are progressing and changing the treatment modalities with very careful documentation to our clinical trials.

COST SAVINGS

Mr. BONILLA. Well, the medical benefits are profound. Tell me now about any savings realized from these advances as well.

Dr. KUPFER. Well, going back to the treatment of premature infants, although there are only about 600 to 700 premature infants a year that fall into this high risk group, if you save an infant from going blind, and that infant lives for 65 or 75 years, you can imagine the accumulated savings. And it does represent tens of millions of dollars every year to the taxpayer.

The diabetic retinopathy studies have shown that with delivery of laser treatment, even if it's only delivered to half the population, which is what we're doing at the present time, we're saving about $1.2 billion a year in costs that would have accrued if these patients had gone blind.

The optic neuritis clinical trial I just mentioned to you is saving about $26 million a year. We did a clinical trial that considered whether matching the recipient of a corneal transplant with the donor in terms of what we call HLA matching, the sort of matching that's done with kidney transplants, might improve the outcome of corneal transplants in very high risk cases. It was shown that it did not help, and that immediately saved the $1,000 in HLA matching costs for every case that's done. And there are about 4,000 of these high risk cases done every year. So that's a considerable savings.

And finally, I was mentioning earlier that we've just concluded a clinical trial in which a particular operation that was proposed for sudden blindness in the elderly and had begun to gain acceptance was shown not to be of any benefit. And by not doing that operation, we're saving somewhere between $30 million and $70 million a year.

Mr. BONILLA. So profound progress on both fronts, then, it sounds like?

Dr. KUPFER. That is correct, sir.

VITRECTOMY

Mr. BONILLA. I'd like to move on to something I was reading about the other day, where ophthalmologists at Hahnemann University in Philadelphia are helping patients regain vision that they had lost due to diabetes or aging. And looking at some of the details, it's just phenomenal to read about how you use these apparently tiny, tiniest of instruments to perform the surgery that dissects scar tissue from the surface of the retina, and the tissue of the back of the eye that plays a role similar to the film in a camera.

Dr. KUPFER. Yes, sir.

Mr. BONILLA. What can you tell us about the procedure, and I hope I pronounce it right, because I had not heard of it before, called vitrectomy.

Dr. KUPFER. Vitrectomy, yes, sir.

Mr. BONILLA. I understand the procedure is, well, I want you to tell me about the procedure, and tell me whether NEI had anything to do with developing this procedure.

Dr. KUPFER. Yes, sir. The back of the eye, the space between the lens and the retina is filled with a jelly-like material called vitreous. And until 1970, one of the complications of surgery of the eye was to lose vitreous. In 1970, 1971, 1972, with the support of the National Eye Institute, an ophthalmologist who at that time was in Miami decided that if there was inflammatory debris in the vitreous, or if there were new vessels in the vitreous, or if there was blood in the vitreous, why not remove that diseased vitreous and replace it with an artificial vitreous.

It was the introduction of this operation called vitrectomy, which was supported by the National Eye Institute in the early 1970s that came into vogue. And suddenly we realized that we were able to treat a large number of patients quite successfully, who otherwise would have been blind by removing this abnormal vitreous.

Once the instrumentation was developed, which we also supported, a whole industry for the production of instruments for vitrectomy arose primarily as a result of that intervention. The surgeons realized that with the proper instrumentation, they could actually peel membranes from the surface of the retina.

Now, just to give you some idea of the difficulty of this, visualize the retina as one sheet of Kleenex. You know, Kleenex comes in two sheets. Just think of one sheet. That's how thick the retina is. And here it is, lying in the back of the eye. And there's a layer of scar tissue. One must take instruments and find a plane to dissect between the retina on the one hand, being careful not to damage the retina, and the scar tissue on the other. Surgeons have now perfected this technique. It's a modification of vitrectomy called membrane stripping.

So I think this not only is an example of how knowledgeable and how advanced ophthalmic surgeons can be with the right instruments, and this is all done under a microscope, as you might imagine, with internal illumination in the eye. But the whole technology of developing these instruments has been an American initiative.

Mr. BONILLA. It's amazing. I'm just glad you guys are doing that and not me. I'm afraid I'd mess it up.

I'd like to move on to something else. You stated that as the population of the U.S. ages, more and more people will be at risk and will suffer from visual problems. How is NEI specifically addressing this issue and if so, how?

Dr. KUPFER. We are aware of the shifting demography in terms of the aging population. And there are five conditions that are definitely age-related. There's cataract, diabetic retinopathy, glaucoma, macular degeneration and low vision, resulting from these four diseases. We have placed high priorities on looking at these five conditions. And we are working very hard in terms of basic research, in both genetics and molecular biology of these diseases as well as some clinical trials in cataract and macular degeneration. This is a very high priority for us.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. BONILLA. In your budget justification, you talk about the National Eye Health Education Program and three related studies specifically targeted to at-risk populations. Is the culture-specific campaign for Hispanics with diabetes one of the three? Also, what progress has been made in this area?

Dr. KUPFER. Yes, sir. I'm very happy to report that we have begun to target Hispanics in this National Eye Health Education Program. We had to develop the material first, and now we are in the process of tailoring it. To do this, we thought the appropriate thing to do would be to begin with focus groups. And we had eight focus groups conducted across the country. There were groups that were conducted for central Americans in Washington, D.C., for Puerto Ricans in New York City, for Mexican Americans in Los Angeles, and Cuban Americans in Miami.

And as a result of those focus groups, material is being developed, primarily for radio and television, to reach these communities in the language and with the sensitivity to the culture that they represented. These activities are now ongoing and we will formally launch this part of the National Eye Health Education Program this summer. That will be expanded as we expand the areas of glaucoma and diabetic eye disease, which are the two target areas in the National Eye Health Education Program.

CATARACT

Mr. BONILLA. You said cataract surgery is one of the procedures most reimbursed by the Medicare program. Is it possible that new treatments will be available to reduce this cost in the future?

Dr. KUPFER. Yes, Mr. Bonilla. As a matter of fact, we know that if we could just slow down the development of cataract by 10 years, we'd reduce by about 45 percent the necessary surgery being delivered. And obviously, people would prefer not to have surgery, even the most successful surgery that's ever been developed, and that's cataract surgery.

We're working very hard on the major hypothesis at the present time on the cause of cataract, and that is oxidative damage. There are a number of approaches to this. We're working very aggressively. We not only have the academic community involved, but we're slowly getting the industrial community interested in this. And I think we're going to see some progress made in the next five years.

RESEARCH IMPACT ON U.S. INDUSTRY

Mr. BONILLA. One final question. What potential impact does NEI research have on U.S. industry?

Dr. KUPFER. We think it has a very major impact, and of course, it's always been anecdotal until very recently. And at the suggestion of one of our staff, we began looking at patents that were filed between 1975 and 1993 dealing with anything that had to do with the eye and the visual system. There were actually 8,000 patents.

We then looked at whether NIH was cited as the source of research upon which those patents were based. And about 50 percent of the publications cited as prior art had some NIH attribution. And of those, about half had National Eye Institute attribution. So I think we have a major impact on the development of commercially viable products. I think this bodes well for the economic stability of the American industry. We will pursue this avenue to get more information that will bear on this question.

Mr. BONILLA. Doctor, I thank you for being here today. It is truly exciting to hear about the things you are doing, and we appreciate the time you and your colleagues have taken to come here today.

Dr. Varmus, you didn't even need to be here for this one. [Laughter.]

Mr. BONILLA. You missed an exciting one yesterday.

Dr. VARMUS. So I heard.

Mr. BONILLA. But at this time we will conclude your hearing, and we appreciate your being here.

Dr. KUPFER. Thank you very much, sir.

[The following questions were submitted to be answered for the record:]

FY 1994-1996 BUDGET

Mr. Porter: Identify FY 94-96 spending on the following: Retinitis Pigmentosa, Glaucoma, Diabetic Retinopathy, Macular Degeneration, Cataract, and CMV Retinitis.

Dr. Kupfer: The following data identifies the funding for Eye Diseases for FY 94-96 (dollars in thousands):

	Fiscal Year		
	FY 1994	FY 1995	FY 1996
Retinitis Pigmentosa	$17,736	$18,367	$18,931
Glaucoma	28,850	29,889	30,829
Diabetic Retinopathy	16,073	16,645	17,156
Macular Degeneration	64,589	66,888	68,941
Cataract	21,521	22,296	22,997
CMV Retinitis	6,621	6,857	7,067

DIABETES

Mr. Stokes: What is the extent of the ocular complications of diabetes in the American population in general and in minorities?

Dr. Kupfer: Diabetes affects approximately 14 million Americans, with the incidence rate higher for African Americans, Hispanics, and Native Americans. More than 2.1 million African Americans have diabetes, about 7 percent of this population. The prevalence of diabetes is two to three times greater for Hispanics than for non-Hispanic whites, affecting about 9 to 10 percent of this population. About 6.3 percent of all American Indians 15 years of age and over have diagnosed diabetes. About half of all people with diabetes have at least mild signs of diabetic retinopathy, the most common ocular complication of diabetes. Diabetic retinopathy is the leading cause of blindness in adults 25 to 74 years of age. As many as 25,000 people go blind each year, including as many as 6,300 new cases of blindness for African Americans. Unfortunately, there is little information on the complications of diabetes in the Hispanic and Native American populations. However, studies indicate that Hispanics and Native Americans are diagnosed with diabetes at an earlier age than whites, therefore allowing for a longer history of the disease and thus a higher risk of complications such as diabetic eye disease.

DECADE OF THE BRAIN

Mr. Stokes: What is the extent of the Institute's investment in this particular area of research in FY 96? How does this compare with FY 95 and FY 94?

Dr. Kupfer: The NEI will invest $238 million in the "Decade of the Brain" initiative in FY 1996. In FY 1995, the NEI will invest $230 million, and $221 million in FY 1994.

Mr. Stokes: What opportunities are ready to be exploited, and what are the potential benefits for improving the health of the American people?

Dr. Kupfer: Powerful techniques are emerging from the fields of molecular biology, neural imaging, and computational neuroscience to open up numerous opportunities for major advances in understanding basic visual mechanisms and visual disorders. These opportunities include: determining the etiology of myopia (nearsightedness) and identifying the risk factors associated with this and other refractive errors to prevent their occurrence or progression; understanding the neural and motor mechanisms that control eye movements; developing clinically useful diagnostic tests for assessing visual performance, especially in infants and young children; understanding how the visual system is assembled during critical periods of development; and, determining the necessary conditions or successful regeneration following damage by disease or trauma to the adult visual system, and what role transplants might play in repairing these conditions.

GENE THERAPY

Mr. Stokes: Gene Therapy and its latest advances in Gene Therapy techniques appear to offer tremendous opportunity for continued advances in the treatment, early detection, and prevention of diseases and disorders. What opportunities would Gene Therapy or Gene Manipulation Research hold for advances of eye research, such as Glaucoma or Retinal Disease?

Dr. Kupfer: Investigators have identified a number of genetic mutations responsible for causing human ocular diseases, and have developed highly-sophisticated ophthalmic surgical techniques for the relatively easy delivery of materials to diseased cells in the eye. These achievements, and others, have greatly increased opportunities for developing human gene therapy and other treatment strategies to correct or delay the progression of ocular diseases. For example, more than 80 mutations have been identified in several forms of Retinitis Pigmentosa (RP). Investigators have already successfully treated an RP-like condition in an animal model. In addition, familial linkage studies suggest that a single gene is responsible for autosomal dominant juvenile glaucoma.

For human gene therapies to become reality, scientists must develop novel safe and efficient gene transfer systems to achieve therapeutic levels of beneficial gene products. The groundwork has been laid for this kind of research. Suitable tissue culture and animal model systems for development and testing purposes are available now.

CATARACT

Mr. Stokes: What basic research findings have major implications for future cataract treatments, and are there clinical trials underway in this area?

Dr. Kupfer: A substantial proportion of people who undergo cataract surgery develop secondary cataracts, a complication that increases the cost of cataract treatment. Research has shown that secondary cataract formation is the result of a normal response of the residual lens cells that remain after surgery. These cells are biologically programmed to divide and differentiate in response to specific signals. Finding out what these signals are has preoccupied lens developmental and cell biologists. In normal development and throughout life, lens epithelial cells divide and differentiate. This process is essential for lens transparency. Growth factors, such as transforming growth factor and fibroblast growth factor, have emerged as key players in this process. Understanding the process and the role growth factors play in it may provide insights into the causes of secondary cataracts and yield prophylactic measures that reduce this complication. As yet, there are no clinical trials underway in this area.

CLINICAL TRIALS

Mr. Stokes: Clinical Trials are the backbone for bridging basic research and advances in medical treatments. NIH Clinical Trials have yielded significant health benefits for the American people and has yielded comparable economic savings as well. What are the four major clinical trials that are underway at the Institute? What level of funding is included in the FY 1996 budget for clinical trials? How many trials would be funded? How many of these trials are new and how many are ongoing?

Dr. Kupfer: The NEI currently has 17 clinical trials underway. Of these, the major ones would include the Ocular Hypertension Treatment Study, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study, the Collaborative Initial Glaucoma Study, and the Herpes Eye Disease Study. In FY 1996, the NEI will be supporting 14 ongoing clinical trials. Our latest estimates indicate that one or two new clinical trials are possible for FY 1996 such as a large epidemiological evaluation of the extent of the problem of eye disease and an evaluation of the efficacy of medical interventions.

SPIN-OFFS

Mr. Stokes: To what extent has knowledge gained in AIDS research advanced knowledge in other research emphasis areas under the purview of your institute?

Dr. Kupfer: NEI-supported research in this area has centered on the pathogenic mechanisms involved in HIV-associated optic neuropathy and in ocular opportunistic infections, on the development and evaluation of drugs, drug delivery systems, and strategies for treating the ocular complications of AIDS. The basic research efforts have contributed to a better understanding of the fundamental causes and etiologic factors responsible for uveitis. Novel drug delivery systems first used clinically in the treatment of CMV retinitis, may have broader application in treating other retinal conditions.

COST BENEFITS

Mr. Stokes: What have been the major cost savings to the nation as a result of continued investments in Vision Research, Research Training, and Outreach?

Dr. Kupfer: The Nation's continued investment in vision research, research training, and outreach has yielded significant savings over the last several years. NEI-supported research has demonstrated that currently recommended treatments for diabetic retinopathy are over 95 percent effective in preventing blindness. It has been estimated that these treatments save society $1.2 - 1.6 billion in direct and indirect costs per year. The Cryotherapy for Retinopathy of Prematurity Study demonstrated the effectiveness of cryotherapy in halting the progression of the abnormal proliferation of blood vessels in the back of eyes of very premature infants. It is estimated this treatment generates $20 million in government budgetary (indirect) savings each year. The Optic Neuritis Treatment Trial found that oral corticosteroids were not effective in treating optic neuritis, an acute debilitating inflammation of the optic nerve that primarily affects women. Scientists estimated that the annual savings could be approximately $26 million in direct treatment costs. The Collaborative Corneal Transplantation Study showed that donor-recipient tissue matching was not effective in reducing transplant rejection. However, ABO blood group matching was effective in this regard. Had the more costly HLA tissue typing become the standard practice, the cost of corneal transplantation would have risen by about $1,000 per case. The Ischemic Optic Neuropathy Decompression Trial demonstrated that decompression surgery for ischemic optic neuropathy (the most common cause of sudden visual loss in older Americans) was no better than careful follow up and may even be harmful. It is estimated that $30 - $70 million will be saved annually in direct treatment costs by not performing this operation.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 96 Budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years?

Dr. Kupfer: For the NEI, the total number of research projects will fall from 1127 in FY 1986 to an estimated 930 in FY 1996. The success rate will fall from 46.5 percent in FY 1986 to a projected 30.2 percent in FY 1996.

Mr. Stokes: What portion of the Institute's budget is invested in investigator initiated research project grants , and is this percentage consistent with that of the other Institutes, explain?

Dr. Kupfer: In FY 1996, 65.1 percent of the total NEI budget and 75.6 percent of the request for extramural research and training would be devoted to research project grants. The comparable figures for NIH as a whole are much less, 52.9 percent (total) and 67.6 percent (extramural research). Unlike other Institutes, the NEI does not award program project grants or other types of "umbrella" mechanism of research support. Moreover, the NEI does not fund clinical trials or other types of applied research using R01-type mechanisms. The NEI did not issue any Requests for Applications (RFAs) in FY 1994 or FY 1995, and has no plans to do so in FY 1996. Thus, essentially the entire NEI research project grant category supports individual investigator-initiated research. These management decisions have the effect of increasing the NEI success rate relative to that of the other Institutes.

FTEs

Mr. Stokes: Is the Institute currently under a FTE freeze, and if so how long has it been under this freeze? How is it impacting operations?

Dr. Kupfer: The NEI is not currently under a hiring freeze, but was previously under a hiring freeze for approximately one year.

FEDERAL ROLE IN INTRAMURAL RESEARCH

Mr. Stokes: In light of continuing fiscal constraints, in your professional judgement, why must the federal role in Intramural Research continue?

Dr. Kupfer: The intramural research program at the NIH has a number of differences from the extramural program, both in organization and composition, that make it particularly able to efficiently and promptly address important areas of health research. The Warren Grant Magnuson Clinical Center is a critical part of the intramural research program and is a highly specialized patient care facility specifically designed to pursue clinical research. Physicians, nurses, and health care providers are trained in the rigors of clinical trials. Medical records are organized to include data collection forms to accurately record the clinical information needed to assess the efficacy of new treatments. Medical institutions established and organized to provide routine medical care are less efficient environments for the conduct of clinical research. In addition, the Clinical Center is structured so that the basic research laboratories are adjacent to patient care clinics and inpatient hospital beds. This promotes interaction between the laboratory bench and the bedside. In the past 10 years, NEI researchers have taken a number of new therapies from the laboratory and applied them to patient care. Cyclosporine was first used to treat intraocular inflammation in patients at the Clinical Center and is now successfully used to prevent blinding disease in patients throughout the world.

The intramural research program is also organized so that resources can be quickly redirected to address important health problems. This has been extremely critical for the NEI's ability to conduct research in the area of AIDS. Cytomegalovirus (CMV) retinitis is the most common opportunistic infection of the eye in patients with AIDS affecting up to 40% of patients during the course of their disease. Ganciclovir, the first drug approved for the treatment of this disease, was first studied in a series of patients at the clinical center. Similarly, foscarnet, the second drug approved for the treatment of this blinding condition, was also examined in an important trial carried out by the intramural research program. Most recently, an intraocular implant that releases ganciclovir into the eye was first assessed in a randomized clinical trial at the clinical center. These studies would have taken years longer to perform by the extramural community. Finally, the intramural research program and the clinical research program allow for the collection of clinical researchers and basic scientists from a varied array of disciplines to work together on one campus. This association has allowed the NEI to participate with other institutes in following patients on new drugs for the treatment of disorders including cancer, multiple sclerosis, and AIDS. This cooperation lead to the discovery that one new drug for AIDS causes retinal lesions. This adverse effect was undetected by previous drug company-sponsored clinical trials, where there was less rigor in collecting clinical information. The NEI's finding lead to a change in the product insert and included recommendations for the screening of patients treated with the drug.

RESEARCH PROJECT GRANTS

Mr. Stokes: What has been the trend in the average cost of research project grants over the past five years? What is the trend in terms of constant dollars?

Dr. Kupfer: The average annual cost of research project grants, in total, was $179,000 in FY 1992 and has grown to $214,000 in FY 1996. The growth in average cost, over the five years, has ranged from a low of 2.6 percent in FY 1995 to a high of 6.0 percent in FY 1992, with an average increase over the 5 year period of approximately 4 percent.

In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average annual cost of research project grants, was $128,000 in FY 1992 and has grown in constant dollars to $131,000 in FY 1996. The growth in average cost, over the five years, has ranged from a low of -1.4 percent in FY 1995 to a high of 2.1 percent in FY 1994, with an average increase over the 5 year period of approximately 0.4 percent.

Mr. Stokes: What is the success rate for Research Applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Kupfer: The chart below provides numbers of applications submitted, applications funded, and success rates for the five year period from FY 1990 to FY 1994.

Success Rates for Minorities, Women, African Americans, and HBCUs

	Applications Submitted	Applications Funded	Success Rate
Asian	366	98	27%
Hispanic	68	25	37%
Native Americans	3	1	33%
African Americans	25	4	16%
Subtotal	462	128	28%
Women	578	211	37%
HBCUs	6	4	67%

The data given above was collected by the NIH Division of Research Grants. Because of the voluntary nature of the information about gender and race/ethnic origin provided in grant applications, the data is incomplete.

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to women? To minority researchers? To African American Researchers? To HBCUs?

Dr. Kupfer: The chart below provides average costs of research project grants in terms of real and constant dollars for FY 1990 and FY 1994.

Competing Grant Average Costs for Minorities, Women, African Americans, and HBCUs

(Dollars in thousands)

Base Year = 1990

	FY 1990			FY 1994		
	Current	BRDPI	CPI	Current	BRDPI	CPI
Asian	$140	$140	$140	$162	$138	$121
Hispanic	112	112	112	279	237	208
Native Americans	N.A.			N.A.		
African Americans	113	113	113	177	151	132
Subtotal	136	136	136	190	161	141
Women	155	155	155	190	161	141
HBCUs	162	162	162	285	243	212

The current dollar data above was collected by the NIH Division of Research Grants. Because of the voluntary nature of the information about gender and race/ethnic origin provided in grant applications, the data is incomplete.

DIABETIC RETINOPATHY

Ms. Lowey: Can you update the Committee on this initiative?

Dr. Kupfer: The NEI and the Juvenile Diabetes Foundation International (JDFI) have initiated a cooperative program of research support. The purpose of this effort is to stimulate basic research activities directed toward discovering the cellular and molecular basis of diabetic retinopathy, and toward the development of biological modifiers or pharmacologic agents that would be useful in preventing or treating this condition. Applications submitted to the NIH will be assigned and reviewed according to the usual NIH peer review procedures. Meritorious applications not funded by the NEI will be considered by the JDFI for possible funding. The mechanism of NEI support for this program will be the research project grant (RO1) or FIRST (R29) award. the NEI and the JDFI plan to make several competing awards in each of the next few years.

NEURITIS AND MULTIPLE SCLEROSIS

Ms. Lowey: This seems to me an incredibly important discovery. Multiple Sclerosis is a horrible disease that affects too many women and their families. Could you tell us more about this discovery? Where might this lead us in preventing the onset of Multiple Sclerosis?

Dr. Kupfer: The Optic Neuritis Treatment Trial (ONTT) enrolled 457 patients with unilateral optic neuritis with visual symptoms of eight days or less. Approximately 77 percent of these patients were women. The patients were randomly assigned to receive one of the following treatments: intravenous methylprednisolone for 3 days followed by oral prednisone for 11 days; oral prednisone for 14 days; or, oral placebo for 14 days. Among the 389 patients who at the time of entry into the ONTT were not diagnosed as probable or definite multiple sclerosis (MS) based on clinical criteria, the intravenous group had a lower rate of development of clinically defined MS within the first two years than did the placebo or prednisone groups. Most of the beneficial treatment effect on the neurologic course was manifested in the patients with an abnormal MRI scan at study entry. However, by the end of the third year of follow up, the cumulative incidence of definite MS in each group was similar. Some clinicians feel that retreatment with intravenous corticosteroids or other agents could prolong the beneficial effect. However, at present there is no direct evidence to support this.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

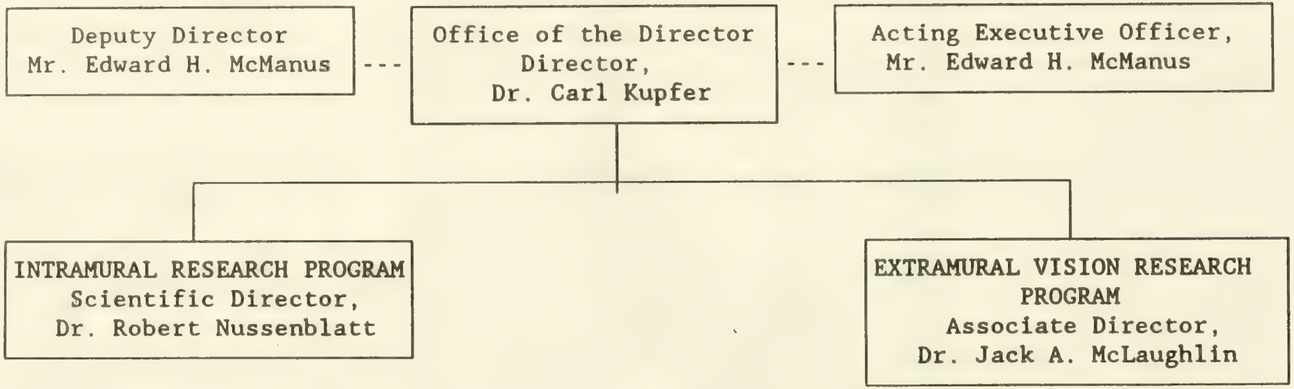
FY 1996 Budget	Page No.
Organization chart	46
Appropriation language	47
Amounts available for obligation	49
Budget mechanism table	50
Summary of changes	52
Budget authority by object	54
Administrative costs	56
Significant items in House and Senate Appropriations Committee Reports	57
Authorizing legislation	62
Appropriation history	63
Budget authority by activity	65
Justification:	
A. General statement	67
B. Extramural research	70
C. Intramural research	79
D. Research management and support	82
E. Detail of full-time equivalent employment (FTE)	84
F. Detail of end-of-year employment	85

46

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Organization Structure



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Dr. Carl Kupfer

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Mr. Edward H. McManus

INTRAMURAL RESEARCH PROGRAM
Scientific Director,
Dr. Robert Nussenblatt

EXTRAMURAL VISION RESEARCH PROGRAM
Associate Director,
Dr. Jack A. McLaughlin

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders, [$291,600,000] $300,693,000.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation..................	$290,260,000	$291,600,000	$300,693,000
Section 205 Procurement reduction.....................		(138,000)	
Section 207 Rent reduction......		(7,000)	
Section 513 S&E reduction.......		(115,000)	
Subtotal, adjusted appropriation................	290,260,000	291,340,000	300,693,000
Comparative transfer to: Office of AIDS Research, NIH for HIV Activities.........	(8,381,000)	---	---
Comparative transfer from other NIH Institutes for Management Fund adjustment.....	+581,000	+617,000	---
Subtotal, adjusted budget authority.............	282,460,000	291,957,000	300,693,000
Unobligated balance, lapsing......................	(354,000)	---	---
Total obligations............	282,106,000	291,957,000	300,693,000

1/ Excludes the following amounts for reimbursements activities carried out under this account: 1994 - $11,000,000; 1995 - $12,000,000; and 1996 - $12,000,000.

Also excludes funding for HIV activities: FY 1995--$8,633,000; FY 1996--$9,125,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research projects						
Noncompeting...........	665	$134,695,000	720	$146,863,000	713	$149,598,000
Admin. Supplemantal....	(22)	1,065,000	(22)	1,000,000	(22)	1,519,000
Competing..............						
Renewals..............	158	34,477,000	111	30,010,000	115	28,261,000
New...................	119	19,538,000	114	17,092,000	89	16,227,000
Supplemental..........						
Subtotal, competing	277	54,015,000	225	47,102,000	204	44,488,000
Subtotal, research projects...............	942	189,775,000	945	194,965,000	917	195,605,000
SBIR/STTR...............	33	3,850,000	47	5,342,000	40	5,600,000
Total, research projects...............	975	193,625,000	992	200,307,000	957	201,205,000
Research Centers						
Core/specialized.......	30	8,076,000	30	8,344,000	30	8,694,000
Other Research:						
Research Career prog...	17	1,358,000	20	1,765,000	25	2,216,000
Cooperative clin. res..	154	23,422,000	156	24,200,000	188	29,177,000
Biomedical research support...............						
Minority biomedical support...............		151,000		364,000		375,000
Other res. related.....	17	931,000	13	451,000	13	464,000
Subtotal, other res...	188	25,862,000	189	26,780,000	226	32,232,000
Total, research grants..	1,193	227,563,000	1,211	235,431,000	1,213	242,131,000

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Training:						
Individual awards						
Noncompeting...........	54	$1,568,000	55	$1,648,000	55	$1,696,000
Competing..............	40	1,032,000	40	1,085,000	40	1,116,000
Subtotal, individual awards...............	94	2,600,000	95	2,733,000	95	2,812,000
Institutional awards						
Noncompeting...........	144	4,084,000	152	4,147,000	152	4,267,000
Competing..............	23	609,000	23	618,000	23	636,000
Subtotal, institutional awards...............	167	4,693,000	175	4,765,000	175	4,903,000
Total training..........	261	7,293,000	270	7,498,000	270	7,715,000
Research & development contracts..............	19	7,775,000	25	8,123,000	26	8,859,000
	FTEs		FTEs		FTEs	
Intramural research.....	186	28,937,000	182	29,637,000	179	30,420,000
Research management and support................	67	10,892,000	68	11,268,000	68	11,568,000
Extramural Construction						
TOTAL...................	253	282,460,000	250	291,957,000	247	300,693,000
Clinical Trials		(26,002,000)		(26,983,000)		(27,238,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

52

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Summary of Changes

1995	Estimated budget authority	$291,957,000
1996	Estimated budget authority	300,693,000
	Net change	+8,736,000

	1995 Current Estimated Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
Changes:				
A. **Built-in:**				
1. Intramural				
a. Within grade increase		$12,458,000		+$177,000
b. One more day of pay		12,458,000		+48,000
c. Annualization of January 1995 locality pay		12,458,000		+50,000
d. FY 1996 pay increases		12,458,000		+208,000
e. FECF Unemp. Comp.		12,458,000		+1,000
f. Payment for Mgmt fund		8,622,000		+336,000
g. Service and supply fund increase		8,557,000		+276,000
Subtotal				+1,096,000
2. Research Management & Support:				
a. Within grade increase		4,588,000		+65,000
b. One more day of pay		4,588,000		+18,000
c. Annualization of January 1995 locality pay		4,588,000		+19,000
d. FY 1996 pay increase		4,588,000		+75,000

	1995 Current Estimated Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
e. FECF Unemp. Comp.	0	4,588,000		+1,000
f. Payment for Mgmt fund		2,305,000		+97,000
g. Service and supply fund increase		3,469,000		+140,000
h. DHHS Working Capital Fund decrease		291,000		-8,000
i. FTS decrease		615,000		-19,000
Subtotal				+388,000
B. Program:				
	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	720	147,863,000	-7	+3,254,000
b. Competing	225	47,102,000	-21	-2,614,000
c. SBIR/STTR	47	5,342,000	-7	+258,000
Total	992	200,307,000	-28	+898,000
2. Center grants	30	8,344,000	---	+350,000
3. Other research	189	26,780,000	+37	+5,452,000
4. Training	270	7,498,000	---	+217,000
5. Research and development contracts	25	8,123,000	+1	+736,000
	FTE		FTE	
6. Intramural research	186	29,637,000	-3	-313,000
7. Research management and support	67	11,268,000	---	-88,000
Subtotal				+7,252,000
Total changes				+8,736,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment...............	250	247	-3
Full-time equivalent of overtime and holiday hours............	---	---	---
Average ES salary...........	$113,000	$115,000	+$2,000
Average GM/GS grade.........	10.6	10.6	---
Average GM/GS salary........	$46,000	$46,000	---
Average salary, grade established by act of July 1, 1944 (42 U.S. C. 207)...........	$72,300	$73,700	+$1,400
Average salary of ungraded positions.........	N.A.	N.A.	---
Personnel compensation:			
Permanent positions........	$8,780,000	$8,632,000	-148,000
Positions other than permanent.................	3,389,000	3,507,000	+118,000
Other personnel compensation...............	438,000	453,000	+15,000
Special personnel services...................	1,590,000	2,020,000	+430,000
Total personnel compensation..............	14,197,000	14,612,000	+415,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Personnel benefits..........	2,796,000	2,796,000	---
Benefits for former personnel.................	36,000	13,000	-23,000
Travel and transportation of persons...................	438,000	456,000	+18,000
Transportation of things....................	75,000	78,000	+3,000
Communications, and miscellaneous charges...................	595,000	600,000	+5,000
Printing and reproduction...............	241,000	242,000	+1,000
Other Services:			
Consultant services.......	244,000	244,000	---
Other Services............	1,863,000	2,008,000	+145,000
Purchases from Govt. Accts....................	15,631,000	15,958,000	+327,000
Operation of GOCOs........	44,000	46,000	+2,000
R&D Contracts.............	8,123,000	8,859,000	+736,000
Supplies and materials..................	3,402,000	3,538,000	+136,000
Equipment..................	1,343,000	1,397,000	+54,000
Grants, subsidies and contributions.............	242,929,000	249,846,000	+6,917,000
Total, budget authority by object.......	291,957,000	300,693,000	+8,736,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Administrative Costs

	1995 Current estimate	1996 Estimate	Increase or Decrease
Personnel Compensation: Full-time Permanent (11.1)....................	$8,780,000	$8,632,000	-$148,000
Other than Full-Time Permanent (11.3)..........	3,389,000	3,507,000	+118,000
Other Personnel Compensation (11.5)......	438,000	453,000	+15,000
Special Personnel Services (11.8)..........	1,590,000	2,020,000	+430,000
Total Personnel Compensation (11.9)......	14,197,000	14,612,000	+415,000
Civilian Personnel Benefits (12.1)....................	2,796,000	2,796,000	---
Benefits for Former Personnel (13.0)..........	36,000	13,000	-23,000
Travel (21.0)..............	438,000	456,000	+18,000
Transportation of things (22.0)............	75,000	78,000	+3,000
Communications, utilities, and miscellaneous charges (23.3)...........	595,000	600,000	+5,000
Printing and reproduction (24.0).......	241,000	242,000	+1,000
Consultant services (25.1).	244,000	244,000	---
Other Services (25.2)......	1,863,000	2,008,000	+145,000
Purchase of goods and services from Government Accounts (25.3)...........	13,904,000	14,115,000	+211,000
Operation of GOCOs (25.4)..	44,000	46,000	+2,000
Supplies and materials (26.0)..........	3,402,000	3,538,000	+136,000
Total....................	37,835,000	38,748,000	+913,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1995 House Report	Action Taken or to be Taken
Age-Related Macular Degeneration	
1. The House in its report 103-553, page 56, stated "The Committee supports NEI's molecular genetic research on inherited macular degenerative disease in order to characterize the genes responsible for this condition as well as the more prevalent age-related macular degeneration."	1. Several inherited macular degenerative diseases share significant similarities to the more prevalent age-related macular degeneration (ARMD). NEI-supported investigators are searching for and characterizing the defective genes in families affected by these diseases. These scientists have made great progress in locating the genes for several forms of inherited macular degeneration. As more is learned about the genetic mechanisms which regulate the growth and maintenance of the photoreceptor cells of the retina in health and in disease, this information should be applicable to understanding the pathogenesis of ARMD.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1995 House Report	Action Taken or to be Taken
Diabetic Retinopathy	
2. The House in its report 103-553, page 56, stated "The Committee urges NEI to continue to emphasize diabetic eye research and to work toward eliminating the disproportionately ill effects of diabetes on minority groups. The Committee also encourages the Institute to consider expanding clinical and health services research on eye care and diabetes."	2. Basic and applied clinical research on diabetic retinopathy are very high priorities for NEI. A strategy for addressing many of the promising opportunities for research on diabetic retinopathy is presented in Vision Research - A National Plan: 1994-1998, a planning document developed by the National Advisory Eye Council. Several important projects have been initiated recently in cooperation with the NIH Office of Minority Health. The NEI, for example, has significantly increased funding and expanded the scope for a project in Oklahoma to increase the awareness of Native Americans with diabetes of the eye complications associated with the disease. Another funded study, being conducted in New Jersey, aims to assess risk factors for the development of diabetic retinopathy in African Americans with Type 1 diabetes.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1995 House Report	Action Taken or to be Taken
National Eye Health Education Program (NEHEP)	
3. The House in its report 103-553, page 56, stated "The Committee supports this education program for those at highest risk for eye diseases: African Americans, Hispanics, and the aged."	3. The NEI, through the National Eye Health Education Program, is conducting public and professional education activities that will stress the importance of early detection and timely treatment of diabetic eye disease and glaucoma. This includes a culture-specific campaign for Hispanics with diabetes, including Spanish language materials. The NEI is also supporting three related studies specifically targeted to at-risk populations for complications of diabetic eye disease. The three studies will evaluate the efficacy of a low cost educational intervention to promote annual eye examinations for African Americans of lower socio-economic status, develop a culture-specific and community-based education program for the prevention of blindness in Native Americans with diabetes, and evaluate programs that are designed to increase the use of ophthalmologic services among people with diabetes.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1995 Senate Report	Action Taken or to be Taken
Decade of the Brain	
1. The Senate in its report 103-553, page 89, stated "The NEI will support research that can make major contributions to the "Decade of the Brain" the potential rewards from visual system affords a superb model of the highest levels of information processing perception and control of eye movements by the brain. These will all be priorities of future NEI neuroscience-supported studies. The eye has and will continue to be at the forefront of investigation aimed at educating the overall structure and functioning of the nervous system."	1. The NEI strongly embraces the joint resolution of Congress, P.L. 101-58, that designated the remainder of the 20th century - beginning on January 1, 1990 - as the "Decade of the Brain". In addition to its ongoing conducted and supported neuroscience research related to the "Decade of the Brain," the NEI has developed a number of scientific and programmatic initiatives to take advantage of the opportunities that may arise from the high Congressional priority given to neuroscience research in the 1990s. The potential rewards from visual neuroscience research are great because the visual system affords a superb model of the highest levels of information processing, perception, and control of movement by the brain. The retina is part of the brain and is connected to it by CNS tracts called the optic nerves. For this reason, the visual system has long been the subject of investigations that have been at the forefront of progress in elucidating the overall structure and functioning of the nervous system.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1995 Senate Report	Action Taken or to be Taken
Diabetic Retinopathy	
2. The Senate in its report 103-318, page 89, stated the "The Committee encourages NEI to continue its research efforts within the funds provided."	2. Basic and applied clinical research on diabetic retinopathy are very high priorities for NEI. A strategy for addressing many of the promising opportunities for research on diabetic retinopathy is presented in Vision Research - A National Plan: 1994-1998, a planning document developed by the National Advisory Eye Council.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Authorizing Legislation

	PHS Act/Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation.......	Section 301	42§241	Indefinite	$293,092,000	Indefinite	$302,103,000
National Eye Institute...........	Section 455	42§851	Indefinite		Indefinite	
National Research Service Awards......	Section 487(d)	42§288	Such sums as necessary	$7,498,000	Such sums as necessary	$7,715,000
Total, Budget Authority...........				$300,590,000		$309,818,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	$179,201,000	$219,091,000	$214,080,000	$216,637,000
1988	184,829,000	234,382,000 3/	231,529,000	224,947,000
1989	229,021,000 4/	223,288,000 5/	229,271,000	234,218,000
1990	223,777,000 6/	240,636,000	241,774,000	239,889,000 7/
1990 Sequester				-3,356,000
1991	247,392,000	254,887,000 8/	258,324,000	253,241,000 9/
1991 Sequester				-3,000
1992	272,260,000	272,260,000	267,229,000	269,300,000 10/
1993	285,133,000	279,102,000	279,102,000	276,188,000 11/
1994	272,201,000	290,260,000	290,260,000	290,260,000
1995 12/	292,022,000	290,199,000	291,886,000	291,340,000 13/
1996 12/	300,693,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH. The Senate Allowance and the appropriation spread the funding among the Institutes, including $104,000 for the NEI.

3/ Does not include funding for AIDS research consolidated at the Secretary's level.

4/ The 1989 request excludes funds for AIDS research and education ($4,947,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $5,620,000 in NRSA training programs not considered.

6/ The 1990 request excludes funds for AIDS research and education ($5,697,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

7/ Excludes enacted administrative reductions of $1,316,000.

8/ Excludes $7,105,000 in NRSA training programs not considered.

9/ Excludes enacted administrative reductions of $6,918,000.

10/ Reflects enacted administrative reductions of $1,702,000.

11/ Reflects enacted administrative reductions of $2,914,000.

12/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

13/ Excludes enacted administrative reductions of $138,000, $7,000, and $115,000.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
EXTRAMURAL RESEARCH												
Vision Research......	---	$224,508	---	$229,891	---	$242,277	---	$251,052	---	$258,705	---	+$7,653
Intramural Research..	200	28,512	202	27,987	186	28,937	182	29,637	179	30,420	-3	+783
Research management and support......	66	10,844	70	11,207	67	10,892	68	11,268	68	11,568	0	+300
Total obligations....	266	263,864	272	269,085	253	282,106	250	291,957	247	300,693	-3	+8,736
Unobligated balance lapsing............		+212		+549		+354		---		---		---
Total, budget authority.....	266	264,076	272	269,634	253	282,460	250	291,957	247	300,693	-3	+8,736

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Eye Institute

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
253	$282,460,000	250	$291,957,000	247	$300,693,000	-3	+$ 8,736,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Eye Institute (NEI). Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Over 25 years ago, as an expression of its concern for the thousands of Americans who were blinded each year by eye diseases and disorders of vision, Congress established the NEI, giving it the broad responsibility to conduct and support research, training, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight and the special health problems of the blind. Subsequently, Congress added health education responsibilities to the mission of the NEI and appropriated funds to allow the institute to increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations.

Because vision plays such an important part in our daily lives, surveys have demonstrated that Americans fear disability from loss of vision most among other disabling conditions. Diseases and disorders of the eye and visual system affect men and women, young and old alike, and cost our Nation an estimated $22.3 billion in direct costs and $16.1 billion in indirect costs each year.

Many diseases of the eye and visual pathway, such as age-related macular degeneration, diabetic retinopathy, cataract, and glaucoma are major causes of blindness and visual impairment among older Americans. At a time when great progress has been made in extending the healthy lives of our citizens, these diseases continue to have pronounced effects on quality of life, the ability to act independently, and many other activities that we consider routine daily tasks.

Important progress has been made in a number of areas of vision research that are directed toward the prevention or treatment of disease and associated visual disability. This progress has resulted in many new opportunities for further advancement. The following are some of the many research opportunities that will be pursued in FY 1996:

- Age-Related Macular Degeneration. The identification of genetic, metabolic, and other age-related changes in the retina which contribute to the development of macular degeneration; exploration of transplantation techniques, use of growth factors, and other approaches for rescuing degenerating retinal cells; and, the characterization of biological factors and inhibitors to prevent or retard the development of abnormal choroidal blood vessels in this disease.

- Retinitis Pigmentosa (RP). The exploration of the molecular mechanisms by which known gene defects in various forms of RP produce the disease, and the development of gene therapy approaches for RP.

- Diabetic Retinopathy. Basic research on the cell biology of the retina, including growth factors which appear to play an important role in the development of abnormal and destructive retinal blood vessels; and, the development of new drugs and molecular genetic techniques to inhibit aldose reductase activity, as accumulating evidence indicates that this enzyme is involved in the pathogenesis of the disease.

- Cataract. Investigations of how to augment the lens' natural defense mechanisms which prevent or retard cataract formation; studies to determine how the genetic expression of lens-specific proteins is regulated, and biochemical studies to determine the critical changes in lens proteins which occur with age.

- Glaucoma. Characterization of the "glaucoma" gene; investigations of the molecular mechanisms of fluid production and transport in the eye; determination of the cause of optic nerve damage in glaucoma; research to determine why the rate of glaucoma is higher and the disease possibly more severe in African Americans; the development of better noninvasive methods for evaluating optic nerve status; and, the development of new drugs and biologics to control intraocular pressure.

- Decade of the Brain. Investigations of the normal and abnormal development, and the regenerative capacity of the visual system following injury; molecular mechanisms which produce myopia; visual neural processing; and, the control of eye movements.

The FY 1996 request of $300,693,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Eye Institute during the last five years has been as follows:

	Amount	FTE
FY 1991	$247,765,000	236
FY 1992	264,076,000	266
FY 1993	269,634,000	272
FY 1994	282,460,000	253
FY 1995	291,957,000	250

Purpose and Method of Operation

The NEI is the principal NIH component responsible for conducting and supporting basic and clinical vision research, vision research training, and eye health information dissemination activities. Extramural research is supported primarily through research project grants. Other mechanisms of support include center core grants, cooperative clinical (trial) research grants, R & D contracts, research training, and research career development awards. The NEI maintains an active intramural research program conducted by an internationally recognized team of scientists at its laboratory and clinical facilities located on the NIH campus in Bethesda, Maryland. Research activities of the institute continue to be guided by the goals and objectives in Vision Research--A National Plan: 1994-1998, the most recent in a series of long-range plans developed by the NEI and the National Advisory Eye Council, in conjunction with the vision research community.

Overall Budget Policy

The NEI FY 1996 budget request is $300,693,000, an increase of $8,763,000 or 3.0 percent compared to the FY 1995 level. At the request level, the Institute will support 713 noncompeting research project grants at $149,598,000 and 204 new and competing renewal research grants at $44,488,000, compared to 720 and 225, respectively, in FY 1995. A total of 30 centers will be supported in FY 1996 at $8,694,000. The other research grants category will be supported in FY 1996 at $32,232,000 for 226 awards. This request also includes $30,420,000 for intramural research and $11,568,000 for research management and support. With respect to total FTEs, the FY 1996 request is 247 FTEs as compared to 250 in FY 1995.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

National Eye Institute

EXTRAMURAL RESEARCH

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$242,631,000	$251,052,000	$258,705,000	+$ 7,653,000

Research activities supported by the extramural Vision Research program address the leading causes of blindness and impaired vision in the U.S., including retinal diseases, corneal diseases, cataract, glaucoma, strabismus, and amblyopia. The program seeks to increase our understanding of the normal development and function of the visual system; to determine the causes of, and better diagnose, prevent, and treat sight-threatening conditions; and, to enhance the rehabilitation and quality of life of individuals who are partially-sighted or blind.

Funding for the National Eye Institute during the last five years has been as follows:

	Amount
FY 1991	$212,482,000
FY 1992	224,548,000
FY 1993	230,340,000
FY 1994	242,631,000
FY 1995	251,052,000

Rationale for the Budget Request

The FY 1996 budget request for the extramural Vision Research Program is $258,705,000, a $7,653,000 or 3.0 percent increase over the FY 1995 appropriation. With the requested funding, the NEI will fund highly-meritorious basic biomedical and applied clinical research which will address the leading causes of blindness and impaired vision in the U.S. Following are some of the research activities that will be supported.

Retinal Diseases

The retina, a delicate, light-sensitive tissue at the back of the eye, initiates the process of vision and transmits visual messages to the brain via the optic nerve. Diseases and disorders of the retina and the choroid, the underlying layer of blood vessels that nourish the retina, are the leading cause of blindness in the U.S. These sight-threatening conditions include age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, uveitis (ocular inflammation), and retinal detachment.

Growth Factors in Diabetic Retinopathy. An abnormal proliferation and leakage of retinal blood vessels leading to loss of vision is characteristic of a number of conditions in which the oxygen supply to the retina is obstructed. These conditions include severe diabetic retinopathy, retinal vascular occlusions, and retinopathy of prematurity. Recent studies have demonstrated that a protein called vascular endothelial growth factor (VEGF) is present in greatly increased amounts in the ocular fluid of patients with these conditions. Production of VEGF is also enhanced by experimental procedures which decrease the oxygen supply to the retina. As VEGF is well-known to be capable of stimulating blood vessel growth in the eye, these new studies indicate that VEGF may play a major role in diabetic retinopathy and other ischemic eye conditions. Investigators will expand the search for ways to either block the production of VEGF or to block its ability to stimulate the growth of new blood vessels.

Molecular Genetics of Macular Degeneration. Age-related macular degeneration (ARMD) is the most common cause of severe visual impairment in older persons in the U.S. Approximately 1.7 million Americans have decreased vision from ARMD, and 100,000 are blind from the disease. The prevalence of decreased vision from ARMD is expected to rise to 6.3 million by the year 2030, when an even greater percentage of our population will enter their retirement years. This disease robs otherwise healthy older Americans of their central vision, depriving them of the ability to read, drive, and to enjoy leisure activities that require good vision. There is no effective treatment for the vast majority of individuals with this condition. Since several inherited macular degenerative diseases share significant similarities to ARMD, NEI-supported scientists are searching for defective genes in affected families. Investigators have localized gene mutations to specific chromosomes for three forms of inherited macular degeneration. Interestingly, a mutation in one of these genes causes macular degeneration, while a different mutation in the same gene causes retinitis pigmentosa. The information gained from these studies should help in understanding the cause of the more prevalent ARMD, and scientists are now in a position to expand this type of research.

Molecular Genetics of Retinitis Pigmentosa. Retinitis pigmentosa (RP) is the name given to a group of eye diseases in which the rod and cone photoreceptors in the retina degenerate. More than 100,000 Americans have RP. Individuals with RP typically report night blindness and loss of mid-peripheral vision during adolescence, and are usually legally blind by the age of 40. NEI-supported research has led to significant advances in identifying the molecular defects in several forms of RP. So far more than eighty mutations have been identified in the human gene for the light sensitive pigment, rhodopsin, and mutations in several other genes have been discovered in families with different types of RP. An unusual inheritance pattern of RP has been discovered recently. Several families with RP were identified in which defects in two different photoreceptor genes were necessary to produce the disease. This is a novel finding since in all other RP families studied, one defective gene caused the manifestations of the disease. Increasing attention will now be directed at unraveling the mechanisms by which these gene defects produce RP.

Gene Therapy. One the very first demonstrations of molecular genetic therapy was the curing of a visual defect in an animal model. More recently, using gene transfer technology, scientists have begun to develop methods for the transfer of genes to human ocular tissues. Results of experiments in animal models of RP have demonstrated that adenoviruses vectors can be used to deliver functional genes into the cells of the retina under conditions that neither harm the retina nor produce any systemic toxicity. This is a promising first step and may provide information on the feasibility of this approach in treating patients with retinal degenerations. Scientists will expand these efforts to develop specific and highly-efficient gene delivery systems for use in treating ocular diseases.

Retinopathy of prematurity (ROP). ROP is a serious public health problem which affects low birth weight infants. Cryotherapy was a highly significant advance in the treatment of ROP. However, more infants are now at risk of developing ROP because so many more very low birth babies are being saved in neonatal intensive care units. The NEI is providing funding for the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) Study. This is a multicenter clinical trial to determine if supplemental therapeutic oxygen will reduce the number of infants with prethreshold retinopathy of prematurity that advance to threshold ROP. In addition to ophthalmic outcomes, STOP-ROP will provide neonatal outcome information including data on growth, ventilatory stability, chronic lung disease, neurological maturation, and length of hospital stay. The NEI is collaborating with the National Institute for Child Health and Human Development and with the National Institute for Nursing Research on this project.

Corneal Diseases

Diseases and injury to the cornea are the leading cause of visits to clinicians for eye care in the U.S. and rank among the most painful of eye conditions. NEI-supported research on corneal diseases includes studies of ocular infections and inflammation, problems with tears and the ocular surface, refractive errors, corneal transplantation, and corneal wound healing.

Regulation of Corneal Cell Growth. The endothelium is an important cell layer of the cornea essential for the maintenance of transparency. The corneal endothelium is delicate, has no natural regenerative capacity, and only limited capacity to repair itself following injury. Premature loss of these cells following trauma, surgery, or disease leads to corneal opacification and blindness. NEI-supported researchers have begun to examine the expression of gene products which may regulate growth and differentiation in this tissue. They should be able to learn how growth factors and genes regulate corneal endothelial cell proliferation. This work could lead to methods to rescue damaged corneal endothelial cells and to promote the orderly growth of new cells.

Extended Contact Lens Wear. Contact lenses prescribed for extended wear can lead to several physiological and morphological changes in the cornea. The standard benchmark of safe wear has been to assume that a lack of changes in corneal thickness indicates the absence of alterations in corneal hydration. However, recent work has suggested that corneal thickness measurements are not sufficiently sensitive to predict incipient corneal damage. Contact lens-induced decreases in corneal stromal pH appear to be the underlying cause of lens-induced pathology. Therefore, two new clinical studies will be initiated to examine the range of stromal pH changes which accompany contact lens wear and to develop practical in-office monitoring methods to identify safe conditions for contact lens wear.

Corneal Dystrophy. A number of potentially blinding heritable diseases involve abnormal development of the cornea. The three most common corneal stromal dystrophies share one common characteristic: the deposition of the proteoglycan amyloid. A recent chromosomal linkage study of eight families afflicted with these three diseases found that each distinct condition is independently linked to the same 10 centimorgan region of chromosome five. Thus, they are likely to be different alleles of the same gene. Pathological deposits of amyloid occur in a wide variety of human diseases, ranging from ocular disorders to the devastating neurodegenerative condition, Alzheimer's Disease. None of the 14 human gene products known to be involved in these other amyloid diseases maps to chromosome five. Future work in fine mapping and cloning of the gene responsible for the corneal dystrophies will provide a powerful model system for developing effective therapies for ocular disease and perhaps also for systemic amyloidosis.

Herpetic Eye Disease. More than 500,000 Americans are affected by ocular herpes, which often begins as a painful sore on the surface of the cornea. Like common cold sores, these ocular lesions may periodically recur. The herpes virus can also cause an inflammation deep inside the cornea. An advanced infection of this type is known as herpes simplex stromal keratitis, a condition which can lead to severe corneal scarring, inflammation of the interior of the eye, and even blindness. The Herpetic Eye Diseases Study is currently conducting two clinical trials. The Acyclovir Prevention Trial is evaluating the effectiveness of oral acyclovir in reducing the frequency of recurrent herpetic eye disease in patients with a prior history of the disease. A second trial, The Epithelial Keratitis Trial, is evaluating the effectiveness of oral acyclovir as a preventative agent in stopping the progression of surface (epithelial) disease to the more severe stromal keratitis or iritis.

Radial Keratotomy (RK). Approximately 25 percent of adults in the U.S. have myopia (nearsightedness). Many of these people are candidates for radial keratotomy (RK), a procedure aimed at correcting myopia through surgical incisions made in the cornea. About 250,000 RK surgeries are performed annually in the U.S. The NEI is supporting a multi-center clinical trial to evaluate the short- and long-term safety and efficacy of RK. The five-year follow-up results from the Prospective Evaluation of Radial Keratotomy (PERK) Study indicated that RK is reasonably safe and that few serious complications result from the procedure. However, a problem with RK is the inability to predict the precise outcome for an individual eye. In 1994, the PERK investigators published the results from the ten-year follow-up examination. The data continues to indicate that RK remains a reasonably safe and effective method for correcting myopia. However, more than 40 percent of RK-operated eyes continue to have a gradual shift toward farsightedness. This finding suggests that some people who have RK may need glasses at an earlier age for poor close-up vision, a common problem after age 40, than if they had chosen not to have the surgery. Data on quality of life, symptoms related to glare and fluctuating vision, and subjective visual function remain to be analyzed.

Lens and Cataract

Cataract is an opacity of the lens of the eye that interferes with vision. Cataract is a major public health problem. More than 1.5 million cataract surgical procedures are performed each year at a cost of more than $5 billion. Reimbursements for this surgery account for approximately 12 percent of the entire Medicare Part B budget. The enormous economic burden of cataract will worsen significantly in coming decades as the American population ages. The major goals of this program, therefore, are to determine the causes and mechanisms of cataract formation, to search for ways to slow or prevent the progression of cataract, and to develop and evaluate new diagnostic and therapeutic techniques in cataract management.

Lens Development and Cataract Formation. The lens of the eye consists of elongated transparent lens fiber cells which are derived from another lens cell type, the epithelial cells. Any disruption of the signals that control the formation of lens fiber cells and hence, lens transparency, has implications for cataract formation. Determining exactly what these signals are and how they regulate lens formation continues to be an area of active investigation for NEI-supported scientists. Growth factors, a diverse group of small molecules known to stimulate cell division, have emerged as prime candidates in this regard. Scientists have identified a number of potentially important growth factors including insulin-like growth factor 1 (IGF-1) and fibroblast growth factor (FGF), and have begun to characterize the mechanism of the lens epithelial cell response to these factors. A role in lens development for tumor suppressor genes, the retinoblastoma (Rb) gene and the p53 gene, in the lens has recently been described and will be an area of active investigation.

Epidemiology of Cataracts. Limited information exists on the cause or progression of cataracts. Moreover, the development of each cataract type--nuclear, cortical, mixed and posterior subcapsular--may be influenced by different risk factors. The Lens Opacities Case-Control Study reported that the development of all three cataract types was associated with a lower educational level, and that regular use of a multivitamin dietary supplement decreased the risk of cataract formation. Cortical and mixed cataract types were associated with low dietary intakes of nutrients, Vitamins A, C, and E, riboflavin, niacin, thiamin and iron. The rate of cataract progression and factors affecting this progression are currently being evaluated in the Natural History of Lens Opacities Study. Individuals, free of cataract and those with some lens opacities, will be examined yearly for five years to determine the rate of cataract growth and to define those factors that promote this growth.

Glaucoma

Glaucoma is a group of eye disorders which share a distinct type of optic nerve damage which can lead to blindness. Elevated intraocular pressure is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and the number one cause of blindness in African

Americans. Approximately 3 million Americans have glaucoma, and as many as 120,000 are now blind from this disease. Blindness from glaucoma is estimated to cost the U.S. in excess of $1.5 billion annually in Social Security benefits, lost tax revenues, and health care expenditures. NEI extramural program activities in glaucoma are directed toward understanding the mechanisms of the disease through basic research, identifying risk factors, and preventing blindness.

Molecular Genetics of Glaucoma. We do not understand the molecular and cellular basis of glaucoma. One form of the disease, juvenile onset glaucoma, is characterized by early adulthood onset and elevated intraocular pressure. Its straightforward familial pattern of inheritance (autosomal dominant) makes this an ideal candidate for genetic studies. The juvenile glaucoma gene has been mapped to a region of chromosome 1 extensive enough to contain approximately 20 genes. Once the exact location of this gene is determined, the gene can be cloned and sequenced. The hope is that the DNA sequence of the juvenile glaucoma gene will reveal clues about the fundamental cause of glaucoma.

The most prevalent form of the disease is primary open angle glaucoma (POAG). In complex diseases such as POAG, defects in any one of a number of genes may predispose an individual to the condition which may manifest itself only in the presence of certain environmental stimuli. The NEI is funding two studies designed to identify POAG predisposing genes. Though high-risk, the potential payoff of these and similar future studies could be enormous in terms of understanding the basic pathogenic mechanisms of POAG.

Clinical Trials. The most common treatment for glaucoma is the use of medications to lower intraocular pressure. Although the medications have been demonstrated to be very effective at lowering intraocular pressure, the impact of lowering IOP on preventing visual field loss is not well understood. The economic impact of glaucoma treatment with medications is substantial. Furthermore, IOP lowering medications often have significant side effects and require the patient to adhere to a strict administration schedule, thus potentially having a profound effect on a patient's quality of life.

The NEI has recently initiated three clinical trials designed to evaluate treatment strategies for ocular hypertension and glaucoma. The Ocular Hypertension Treatment Study (OHTS) is designed to determine whether medical reduction of intraocular pressure prevents or delays the onset of visual field loss and/or optic disc damage. Fifteen hundred ocular hypertensive individuals, including a minimum of 375 African Americans, are being assigned randomly to either close observation or to a stepped medical regimen. Participants will be followed for a minimum of 5 years.

The Early Manifest Glaucoma Trial (EMGT) is designed to determine whether and to what extent reduction of intraocular pressure influences the course of chronic open angle glaucoma. The EMGT investigators will study 300 patients with newly diagnosed disease. Patients are being randomized to receive pressure-lowering treatment or to observation with no or delayed treatment. Both groups will be followed very carefully for four years to detect progression of visual field loss and to detect changes in the optic nerve.

Filtration surgery is also effective in controlling intraocular pressure. When successful, filtration surgery may provide the most effective long-term, consistent control of intraocular pressure with the least likelihood of requiring supplemental medications. The Collaborative Initial Glaucoma Treatment Study (CIGTS) is designed to compare the efficacy of a medical regimen to filtration surgery as the initial treatment for newly-diagnosed glaucoma. This clinical trial will compare the two treatment strategies in terms of controlling IOP and will specifically investigate the impact of these treatment strategies on the participants quality of life. Recruitment of 600 patients has begun at 11 clinical centers located throughout the U.S.

Strabismus, Amblyopia, and Visual Processing

Developmental disorders such as strabismus, misalignment of the eyes, and amblyopia, commonly known as "lazy eye", affect 2-4% of the U.S. population, and the correction of strabismus is one of the most frequently performed of all surgical procedures. In addition to research on strabismus and amblyopia, the NEI supports research on presbyopia (the age-related inability of the lens to focus on nearby objects), nystagmus (irregular eye movements), and refractive errors. Understanding the many disorders of visual processing requires a more fundamental understanding of the visual nervous system, including the molecular, genetic, chemical, cellular, and integrative processes that underlie visual perception and the control of eye movements. Three million Americans now have chronic visual conditions that are not correctable by eye glasses or contact lenses, and that impair everyday function. Therefore, the NEI also supports research on improving the quality of life of persons with visual impairments by helping them maximize the use of remaining vision and devising aids to assist those without useful vision.

Ischemic Optic Neuropathy Decompression Trial. Non-arteritic ischemic optic neuropathy (NAION) is the most common cause of sudden visual loss in older persons. The NEI recently issued a clinical alert about results from the Ischemic Optic Neuropathy Decompression Trial (IONDT). The IONDT is a randomized, controlled clinical trial that is being conducted at 25 clinical centers nationwide. The IONDT compared the safety and efficacy of optic nerve decompression surgery plus careful followup versus careful followup alone in patients with NAION. Results from this study indicate that decompression surgery was no better than careful followup in terms of improved vision, and possibly worse. Based on these results, the study concluded that optic nerve decompression surgery, a difficult and expensive procedure, is not an appropriate treatment for NAION. Estimates of the annual potential costs savings that will be realized by not performing this operation range between 30 and 70 million dollars.

Neural Processing. The visual nervous system is a dense network of many individual cells and their processes which communicate with each other at specialized chemical junctions. Using a new technique, which employs micro-laser stimulation and microelectrodes, researchers have been able to stimulate selected nerve cells in individual circuits in this dense meshwork of cells. Results from this approach show how individual nerve cells function together. Previously these results were very difficult to obtain because of the inaccessibility of these functional units. Further refinement of this approach could lead to the development of a powerful tool for isolating discrete networks of nerve cells and for learning how they function and organize information.

Guidance System for Individuals Who Are Blind. Scientists and engineers have developed a prototype navigation device that uses signals from satellites to help guide individuals who are blind through unfamiliar neighborhoods. The device integrates signals from global-positioning satellites, a digitized map stored in the memory of a computer, and an electronic compass both worn by the user. Headphones connected to the computer "read out" auditory cues about the location and features of the local environment to the user (for example, "Library here. Bench there"). The satellite input locates the position of the user with an accuracy of one meter. Work is underway to develop this device further with the goal of increasing access and mobility of individuals who are blind or who have low vision.

Development of the Visual System. A fundamental question in the development of the visual system, is how the highly organized cellular patterns and connections among nerve cells in the adult visual system are formed during development. At "birth" these nerve cells apparently receive "instructions" that cause them to migrate relatively long distances through a complex neural environment to specific sites in the brain. Upon arriving at their final destination, these cells make specific connections and acquire specific functions. Researchers, using precisely defined transplantation experiments, have found that nerve cells seem to know exactly who they are. Further, they found the progenitors, or mother cells, actually make decisions about the fate of their progeny, and do so in a way that it is exquisitely sensitive to the local environment. The progenitor cells may be sending signals to one another or receiving signals from other nerve cells that are essential in determining the developmental fates of their offspring. This research is providing us with significant insights into how the complex connections of the brain are formed, and how inappropriate connections are established when this process goes awry.

Visual Physiology and Behavior. How is information processed within the brain, and how does this information processing result in purposeful behavior? These are fundamental, central problems in modern neuroscience research. The visual system may be the best place for asking such questions because of the extensive knowledge we have of its structure and function. Recent experiment in animals has led to the development of experimental paradigms that permit the monitoring and manipulation of neural activity in visual circuits while the animal performs a well-controlled visual discrimination task. This paradigm has been used to gain insight into the neural activity operating from sensory input through the "decision process" to motor output. Nerve cells in visual centers of the brain have been identified which participate in an active decision process in which incoming sensory signals are evaluated and guide a motor response. Understanding how this type of brain activity operates in the visual system will undoubtedly provide an opportunity to understand what goes wrong in a number of disorders of the central nervous system.

Myopia. Recent results from a NEI-supported study suggest a possible genetic link to nearsightedness or myopia. Researchers at the University of California, Berkeley, School of Optometry are conducting the Orinda

Longitudinal Study of Myopia (OLSM), a study of more than seven hundred school children ages 6 to 14. Measurements were made on each child's refractive error, corneal curvature, crystalline lens power, and axial ocular dimensions. Parents reported their own vision status. The investigators found that schoolchildren whose parents are nearsighted have different shaped eyeballs than children whose parents are not nearsighted. Children of myopic parents had longer eyes even before the onset of myopia. These results suggest that the premyopic eye in children with a family history of myopia already resembles the elongated eye present in myopia. The OLSM will provide a wealth of information on ocular and refractive development in children in the years ahead.

National Eye Institute

INTRAMURAL RESEARCH

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
186	$28,937,000	182	$29,637,000	179	$30,420,000	-3	+783,000

The Division of Intramural Research of the NEI has developed a broad multidisciplinary research effort relating to blinding and disabling disorders of vision that integrates laboratory and clinical research in such areas as ocular inflammatory diseases, retinopathy, developmental and degenerative disorders of vision, cataract, and the effects of neurological defects on vision. The Division of Biometry and Epidemiology is also included in this budget activity.

Funding for the National Eye Institute during the last five years has been as follows:

	Amount	FTE
FY 1991	$25,632,000	170
FY 1992	28,530,000	200
FY 1993	29,609,000	202
FY 1994	28,937,000	186
FY 1995	29,637,000	182

Rationale for the Budget Request

The FY 1996 budget request for intramural research is $30,420,000 a $783,000 or 2.6 percent increase over the FY 1995 level. The request represents the net effect of administrative cost and FTE decreases, and increases for mandatory central services requirements and pay raises. Within the amount requested, funds will be provided for research priorities including neuroscience research related to Decade of the Brain, gene therapy research, and cell and molecular biology.

Visual Neuroscience. NEI-supported scientists continue to provide new and important data on the role and function of the visual motor system. A study investigating the control of movement by visual input and the systems in the brain that performs this vital function is underway. Recently scientists tested the hypothesis that the spread of activity in the superior colliculus, a brain structure critical to rapid eye movement, controls the amplitude of such movement. Minute injections of a neurotransmitter inhibitor into the superior colliculus, changed the direction of the eye movement. This suggests that not only the end-point, but the path taken by the eye is influenced by the superior colliculus; this information is profoundly important not only for understanding how the brain controls eye movement but also how it controls movements in general. This remarkable advance in understanding the sensory-motor system creates opportunities to examine new mechanisms of controlling movement and could lead to a better understanding of how to control disease-induced disorders of eye movement control.

Ocular Complications of Diabetes. Research is focused on the role of aldose reductase and its inhibition of ocular complications associated with diabetes. Researchers have developed an animal model (galactose-fed dogs), that develops both the clinical and histological lesions associated with all stages of diabetic retinopathy. Using this model, investigators have conducted studies to image noninvasive cataract formation and to measure the levels of aldose reductase in the lens--in vivo. With this technique, investigators have demonstrated a direct correlation between inhibition of aldose reductase in the lens and the prevention of the retinal pericyte degeneration, which leads to diabetic retinopathy. Scientists have discovered an extremely potent aldose reductase inhibitor and are in the process of characterizing this new treatment for diabetic retinopathy.

Ocular Genetic Diseases and Gene Therapy. Research discoveries on the natural history and the role of the ornithine aminotransferase (OAT) gene in the development of gyrate atrophy, an inherited degenerative retinal disorder, have become the essence of an intensive basic and clinical research initiative. Scientists are conducting research to genetically alter the defective gene and to culture skin tissues, to be used as a transfer vehicle for inserting the altered gene in gyrate atrophy patients. This research may lead not only to an effective therapy for gyrate atrophy, but may be extended to genetic interventions for other blinding genetic disorders.

Retinal Cell and Molecular Biology. Scientists have discovered several genes that may be implicated in macular degeneration, a leading cause of blindness in aging. In addition, a new gene has been cloned that could be the defective gene in Bardet-Biedl's Syndrome, a hereditary disease of blindness and mental retardation. Investigators also have discovered a protein that promotes the survival of neurons within the central nervous system. This protein (PEDF) promotes maturation of photoreceptor-like cells derived from the retina. It also greatly lengthens the life-span of brain neurons in tissue culture experiments. With these characteristics, future research will explore whether PEDF can be used in transplantation procedures that could be helpful in conditions such as Parkinson's Disease.

Ocular Inflammatory Diseases. Cystoid macular edema is a major cause of visual loss in patients with ocular inflammatory diseases, collectively known as uveitis. Over the last three years, clinical scientists have conducted a randomized clinical trial which compared acetazolamide and a placebo in the treatment of uveitic cystoid macular edema. The study recruitment has been completed and the data is being analyzed. Presently, NEI-supported scientists are conducting two other randomized clinical trials for the treatment of uveitis. In one trial, investigators are studying whether a heparin surface-modified intraocular lens induces less inflammatory reaction in the eye than an unmodified intraocular lens in patients with uveitis undergoing cataract extraction. In a second trial, scientists are studying the induction of oral tolerance with retinal antigens as a treatment for severe uveitis.

Immunologic Mechanisms of Ocular Inflammation. Scientists are examining the role of cell adhesion molecules and cytokines in the development of ocular inflammatory disease. Cell adhesion molecules are surface proteins which are important for antigen sensitization and leukocytes' migration to inflammation sites. Researchers are currently investigating compounds that block cell adhesion molecules as a treatment for uveitis. They have been able to inhibit significantly the development of endotoxin-induced uveitis in mice with a single injection of anti-Mac-1 antibody. Research is now underway to develop and test topically administered substances that can block critical cell adhesion molecules. If animal studies are successful, scientists plan to test therapies based on blocking critical cell adhesion molecules and cytokines in clinical trials of uveitis patients.

Lens and Cataract. Scientists are studying an animal model that expresses a viral enzyme (HIV-1 protease) in the lens, causing cataract formation. In addition, scientists are investigating the biochemical and molecular biological changes that occur prior to cataract formation, to identify the first stages of cataract development, as well as alterations of cells that are infected with the HIV-1 virus. Investigators are also examining the physical mechanisms involved in the activity of lens α-crystallin, the longest-lived protein in the body and one known to accumulate a variety of structural modifications. Such modified proteins would generally be expected to aggregate into large particles in the lens causing light scatter, the hallmark symptom of cataract. However, scientists have determined that α-crystallin has the unique ability to prevent protein aggregation in the lens and to preserve lens transparency over decades. Scientists are continuing to study this protein in an effort to stabilize or augment α-crystallin's capacity to maintain lens transparency, thereby preventing certain forms of cataract.

Glaucoma. Scientists have been studying the trabecular meshwork, a tissue in the eye that has been implicated in the development of open-angle glaucoma. In a series of experiments, investigators have analyzed the proteins present in the four quadrants of the normal trabecular meshwork, and are now examining the differences between normal tissue and glaucomatous trabecular meshwork, and the changes that precede glaucoma. Such results would offer important clues on the causes of open-angle glaucoma and may provide the foundation for the development of effective therapies.

Age-Related Eye Disease Study. The most common causes of blindness in the United States are associated with the aging process. NEI epidemiologists have initiated a natural history study to assess the clinical course, prognosis and risk factors of age-related macular degeneration (AMD) and cataract. Further investigation of the risk factors in the development and progression as well as their pathophysiologies may lead to methods for preventing these debilitating ocular disorders. Additionally, the effects of pharmacologic doses of antioxidants--vitamins C and E and beta-carotene--and zinc on the incidence and progression of AMD, and antioxidants on the incidence and progression of lens opacities will be assessed as part of a randomized clinical trial, using the cohort of 4,600 patients developed for the natural history study.

National Eye Institute

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
67	$10,892,000	68	$11,268,000	68	$11,568,000	---	+$300,000

This budget activity provides resources for crosscutting Institute administrative management as well as programmatic functions including the Office of the Director (OD), the Division of Extramural Activities, Division of Basic Vision Research, Division of Collaborative Clinical Research, the Office of International Program Activities, the Office of Administrative Management, the Office of Science Policy and Legislation, and the Office of Health Education and Communication, in which the National Eye Health Education Program (NEHEP) is organizationally located. The OD is the focal point for decision making regarding the overall scientific direction of the NEI. The extramural research components administer the extensive NEI portfolio of basic and clinical research grants, and all research training and collaborative activities. NEHEP, the first federally sponsored nationwide eye health education program, works in partnership with over 50 public and private organizations. The initial focus is on public and professional education programs for glaucoma and diabetic eye disease.

In addition, this budget activity includes support for the National Advisory Eye Council. Together, these RMS components ensure effective and efficient management of extramural and intramural programs, facilitate cooperative academia-industry-government technology transfer both nationally and internationally, and outreach.

Funding for this activity during the last five years has been as follows:

	Amount	FTE
FY 1991	$ 9,651,000	66
FY 1992	10,998,000	66
FY 1993	11,207,000	70
FY 1994	10,892,000	67
FY 1995	11,268,000	68

Rationale for the Budget Request

The FY 1996 request for research management and support is $11,568,000, a $300,000 increase or 2.7 percent increase over FY 1995. The RMS activity provides for the Institute's overall scientific and management direction. This includes program development and analysis, evaluation of the extent of eye diseases, and the management and allocation of resources. Also included in this activity is the programmatic and fiscal management of approximately 1,500 research grants and contracts, annually, by NEI's Extramural Research staff. They are responsible for developing program plans, communicating scientific priorities to the scientific community, evaluating ongoing scientific progress supported by various extramural research mechanisms, and managing the allocation and spending of funds for grants and contracts.

84

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director.......	40	40	40
Intramural Research Program..	186	182	179
Extramural Vision Research...	27	28	28
Total, NEI.................	253	250	247

Average GS/GM Grade	
1991	10.5
1992	10.5
1993	10.5
1994	10.6
1995	10.6
1996	10.6

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Estimate
Executive level I....			
Executive level II...			
Executive level III..			
Executive level IV...			
Executive level V....			
Subtotal......	0	0	0
Total - Exec. Lev. Sal......			
ES-6.................	1	1	1
ES-5.................	1	1	1
ES-4.................	4	4	4
ES-3.................			
ES-2.................			
ES-1.................			
Subtotal......	6	6	6
Total - ES Salary....	$656,700	$692,687	$707,926
GS/GM-15.............	19	19	19
GS/GM-14.............	23	23	23
GS/GM-13.............	12	12	12
GS-12................	20	20	20
GS-11................	34	34	34
GS-10................	0	0	0
GS-9.................	14	14	14
GS-8.................	11	11	11
GS-7.................	18	18	18
GS-6.................	8	8	8
GS-5.................	6	6	6
GS-4.................	0	0	0
GS-3.................	2	2	2
GS-2.................	2	2	2
GS-1.................	0	0	0
Subtotal......	169	169	169

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of End-of-Year Employment (continued)

	1994 Actual	1995 Estimate	1996 Estimate
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	3	3	3
Senior Grade	2	2	2
Full Grade	2	2	2
Senior Assistant Grade			
Assistant Grade			
Subtotal	7	7	7
Ungraded	0	0	0
Total permanent positions	182	182	182
Total positions, end of year........	250	250	247
Total full time equivalent (FTE) employment, end of year........	253	250	247
Average ES level.........	4.5	4.5	4.5
Average ES salary........	109,450	113,000	115,000
Average GS/GM grade......	10.6	10.6	10.6
Average GS/GM salary.....	46,000	46,000	46,000

THURSDAY, MARCH 23, 1995.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

WITNESSES

DR. ZACH W. HALL, DIRECTOR
DR. PATRICIA A. GRADY, DEPUTY DIRECTOR
ANDREW C. BALDUS, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. BONILLA [presiding]. At this time, we'll hear from Dr. Zach Hall, Director of the National Institute of Neurological Disorders and Stroke.

Dr. Hall, welcome. I understand it's your first time to testifying.

Dr. HALL. Yes, it is.

Mr. BONILLA. It's really painless. Just ask Dr. Grady.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Could I take a moment to introduce Dr. Hall? He is one of our brightest recruits to the NIH, and it is with some pleasure that I introduce him to you. He has had a distinguished career, particularly at the University of California San Francisco, where he served with distinction for many years as the director of the neuroscience program, as the chairman of the physiology department, and as my Saturday afternoon running companion. And as you heard from the testimony of Dr. Kupfer, he's already taken a leadership role at NIH in fostering the inter-Institute initiative with respect to decade of the brain.

Mr. BONILLA. Where are you from originally, Dr. Hall?

Dr. HALL. Atlanta, Georgia.

Mr. BONILLA. Very good. So you just went to school in California, then, correct?

Dr. HALL. I went to school on the east coast and in the south, and then I was employed for a while on the east coast, and then migrated to California.

Mr. BONILLA. We're glad you're here.

Dr. HALL. Thank you very much.

Let me introduce Mr. Andy Baldus, who's the Financial Officer of the Neurology Institute, and Dr. Patricia Grady, who's the Deputy Director, and as you know, will soon become the Director of the National Institute of Nursing Research. And Dr. Varmus you know, and this is Mr. Beldon from the Department.

OPENING STATEMENT

As the new Director of the National Institute of Neurological Disorders and Stroke I'm very pleased to appear before this committee for the first time. I came here from California about six months ago, where, as Dr. Varmus indicated, I was for almost 20 years a researcher in the brain, an NIH grantee, a mentor for young students, and an administrative leader in biomedical research.

I came to the NIH because I believe that this is a moment in our history of extraordinary promise for research on disorders of the brain, and because the NIH has been the worldwide leader in performing and sponsoring that research. In my new position as Director of the Neurology Institute, I look forward to working with Members of the committee, with members of the neurology research community, with patient organizations and with the public to advance our understanding of the basic mechanisms of the brain and the ways in which these can contribute to alleviate the suffering caused by diseases of the brain, the peripheral nerves and the muscles that they enervate.

Disorders of the nervous system are among the most common and debilitating in our society. Stroke, epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebral palsy, ALS, or Lou Gehrig's disease, as it's commonly known, brain tumors, and traumatic injury of the brain or spinal cord, almost all of us have family or friends who suffer from one or more of these disorders. People who have difficulty in communication, people who have difficulty in movement, people who have difficulty with memory and thought processes.

Because the brain is so complex, and because it has limited ability to repair itself, these diseases are among the most intractable in our society. Thus, patients with neurological disorders often live for years with severe and disabling problems resulting in special personal burdens for their family and friends, and financial burdens, both for their families and for society at large.

I believe that the treatment of neurological disease is actually on the verge of undergoing a dramatic change. Continuing advances in our understanding of the brain are paving the way toward the development of new treatments that have the promise of helping millions of Americans. I believe that we're on the threshold of an era in which neurology will not be simply a specialty of diagnosis, as it has often been, but will be a specialty in which successful treatment of brain disorders will be the rule and not the exception.

What I'd like to do today is to highlight research in three areas that are sponsored by the NINDS. First, I'd like to talk about the direct testing of medications and procedures that help people avoid or recover from brain disorders. Let me begin with stroke. Stroke is the third leading cause of death in this country, and the leading cause of disability. Each year there are 500,000 new cases of stroke, about 150,000 of whom die.

Recent clinical trials have suggested two ways in which strokes can be prevented for those at risk. First, a recent clinical trial sponsored by the NINDS showed that for patients with a narrowing of the main artery that leads to the brain, supplying blood and nutrients, surgical intervention to clear the artery can cause a dramatic reduction in stroke, even in patients without visible symptoms.

A second example concerns atrial fibrillation, which is a disorder in the rhythm of the heart beat that also is a major cause of stroke. NINDS researchers have found that for most people with this condition who are under 75 years old with no other major risk factors, the common drug aspirin provides excellent protection with very little risk. This is important, because the alternative to aspirin is a drug that is both more expensive and that carries with it greater risk for complication.

In other research, we're sponsoring a clinical trial to determine whether the hormone estrogen can prevent stroke in post-menopausal women. Widespread application of these treatments thus has the potential to save thousands of Americans from stroke and from the disability that it brings.

NINDS research has also made a difference in the treatment of the youngest Americans affected by brain disorders, very low birthweight infants. These are usually born prematurely and weigh less than three pounds. They're really quite tiny. Dr. Kupfer in his testimony mentioned some of the medical problems that they have.

Medical problems that specifically affect the brain are two that I want to talk about. First, these tiny infants are at risk for bleeding in the brain, and when this bleeding is severe, it can lead to permanent damage and disability. Last year, results from a clinical trial demonstrated that a common medication, indomethacin, given 6 to 12 hours after birth, can dramatically reduce the incidence, the severity of bleeding, and reduce the incidence of lifelong disability.

Now, these very low birth weight babies are also at risk for cerebral palsy. They have about a 20-fold greater chance of getting cerebral palsy than normal birth weight infants. In fact, these very small babies contribute up to 30 percent of the total cases of cerebral palsy in the United States. Thus they make a significant contribution to the problem of cerebral palsy. An NINDS scientist has recently found that a common chemical, magnesium sulfate, given to mothers before the birth of low birthweight infants, has the potential of reducing almost completely the incidence of cerebral palsy.

Modern medical science is often accused of fostering high technology solutions to problems of health care and in fact, by its very success, increasing the costs of medical care to our society. Our ability to improve the survival of people with stroke, with brain injury, or indeed of these very low birthweight infants, which has been one of the triumphs of medical science, could be argued to increase the number of people with expensive disabilities in our society.

My own view is that this is a short-term view. In two of the examples described above—stroke and low birthweight infants—simple common medications have the potential to prevent diseases leading to lifelong disability.

So we think that as research continues and that as our knowledge advances that we can expect to find better, more cost effective solutions to problems so that patients can not only survive, but can go on to live healthy, independent and productive lives.

Now, I'd like to turn from the immediate question of patient care to discuss two scientific issues that are not directly related to patient care at the moment, but that I believe offer great promise for future research. The first of these concerns neurogenetics. As you heard this morning from my colleague, Dr. Francis Collins of the National Center for Human Genome Research, one of the marvels of our scientific age is the ability to find and identify genes that are defective in particular diseases.

The nervous system is an extraordinarily complex organ. It expresses more different genes than any other organ in the body, and so it's perhaps no surprise to find that over 25 percent of all the genetic diseases are estimated to be diseases that affect the nervous system. Many of these are diseases that are familiar to us: Huntington's disease, some forms of ALS, neurofibromatosis, spinocerebellar ataxia, familial Alzheimer's disease, muscular dystrophy and some types of epilepsy, just to name a few of them. Now, to date, the defective gene has been found and identified in over 50 neurological disorders. Yet, finding the gene is only the first step in understanding a disease and in devising suitable therapies for it.

For example, one of the recent exciting discoveries in neurogenetics has been the discovery that a similar type of genetic disorder, something called a trinucleotide repeat, is the basis of the defect in several different neurological diseases. These include myotonic dystrophy, spinobulbar muscular atrophy, Huntington's disease and several others. In each case, what happens is that a tiny portion of the genome becomes repeated over and over and over again. What we don't understand is why that defect leads to neuropathology. In some cases, the issue seems quite mysterious, as the defective gene appears to exert a dominant effect over the normal gene.

As you can see from this example, even when a defective gene is discovered and even when we know what's wrong with it, much remains to be done to understand how the defect leads to disease. This is important, because gene replacement therapy will not be feasible or will not be effective in every case. So we would like to understand the process by which the defective gene leads to disease, with the hope that we could intervene in that process in some way to compensate for the defect that's been caused by the errant gene.

This, then, becomes a problem in neural cell biology as we try to understand both the intracellular and extracellular circuitry of the nervous system to determine how gene expression brings about these disorders. One powerful tool to help us in these studies, provided by molecular genetics, is our ability to develop animal models of particular diseases. For example, NINDS-supported scientists found in 1993 that a gene responsible for many cases of Lou Gehrig's disease (ALS) encodes a particular enzyme that destroys the deleterious by-products of cellular metabolism.

This discovery has now led to the production of a mouse model of the disease. Thus one can look at the gene defect in humans, take a mouse gene and put that same defect in it, and then transfer the altered gene into a mouse, producing a strain of mice that has a disease that's very similar to ALS. This is of enormous importance, because what it means is that one can then study very carefully in the mouse the progress of the disease. One can try out therapies in the mouse, so this is an enormous boon to research in this area.

Let me now then turn to the third area that I want to talk about, and that is what we might call the life and death of nerve cells. In many brain diseases, and included among them are Alzheimer's, Parkinson's, Huntington's, and ALS, particular populations of cells die for reasons that we don't understand. In other cases, such as stroke, cells deprived of oxygen die or in traumatic brain and spinal cord injury, damaged cells die. In these cases, in which large numbers of cells die at the same time, we know that the damaged and dying cells release chemicals which then cause a subsequent, secondary wave of cell death.

Cell death is a serious matter in the nervous system, because unlike the liver, which can regenerate cells, cell death in the nervous system represents a permanent loss. Cells do not divide, they repair themselves poorly, they do not regenerate, and so therefore any loss is a loss for life.

What we would like to know, then, is why do cells die in these particular diseases, and what can we do to help them. Recent research tells us that nerve cells are not passive victims in this process, that in fact they have mechanisms to fight back, to help them survive. And we also know that they have, interestingly, separate mechanisms by which they can actually kill themselves, suicide programs, we might call them, that are important during the development of the nervous system.

We also know that external factors secreted by other cells can cause particular cells to live, and can support their survival. So what we would like to know, then, is how do neurons direct their own survival and that of their neighbors, and how can we intervene in such a way as to promote and help these cells as they fight back against injury, and how can we suppress the pathways and networks that lead to cell death.

Thus, one day we hope to be able to delay the progression of stroke or trauma to the nervous system, and to restore the function of nerve cells that have been damaged. Much work remains to reach that point, but our progress over the last 20 years has been remarkable, and leads us to hope that neurological disease will indeed become the arena for therapy and recovery that we hope for.

Mr. Chairman, Mr. Bonilla, the fiscal year 1996 budget request for this Institute is $648,255,000. I would be happy to answer any questions that you have.

[The prepared statement and biography of Dr. Zach Hall follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Neurological Disorders and Stroke

Mr. Chairman and Committee Members:

As the new Director of the National Institute of Neurological Disorders and Stroke, I am pleased to appear before the Committee for the first time. I have come to the National Institutes of Health (NIH) from the University of California where I had almost twenty years of experience as a laboratory researcher and grantee of NIH, as a mentor to young scientists, and as an administrative leader of biomedical research. I came to the NIH because this is a moment in our history of exceptional promise for research on disorders of the brain, and because NIH is the world-wide leader in performing and sponsoring that research. In my new position as Director of this Institute, I look forward to working with you, with the neurological research community, with patient organizations, and with the public toward our common goal of advancing knowledge that will improve the prevention, diagnosis and treatment of diseases of the brain, spinal cord, and peripheral nerves.

Disorders of the nervous system are among the most common and debilitating in our society. Stroke, epilepsy, Alzheimer's disease, multiple sclerosis, cerebral palsy, Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease, brain tumors, and traumatic injury of the brain or spinal cord--most of us have family or friends with one of these disorders--someone who has difficulty with memory, with movement or with communication. Because the brain is so complex and because it has limited ability to repair itself, these diseases are among the most intractable that afflict mankind. Thus, patients with neurological disorders often live for many years with severe disabilities, resulting in special personal and financial burdens for their families and for society.

The treatment of neurological diseases, however, is on the verge of fundamental change. Dramatic and continuing advances in our understanding of the brain are paving the way toward the development of new treatments that will offer hope to millions of Americans. I believe that we are on the threshold of an era in which successful treatment of brain disorders will become commonplace rather than the exception.

Today I will highlight recent advances in three areas and indicate their future promise. The first is in the direct testing of medications and procedures that help people avoid, or recover from, brain disorders. Stroke is the third leading cause of death in the American population and the leading cause of disability; each year there are over 500,000 new cases. During the past year, findings from a major clinical trial show that in patients with a partial blockage of an artery that carries blood to the brain, surgery to clear the artery is effective in preventing strokes, even if the patient has no symptoms. Stroke, however, has many causes and no single medication or treatment will be effective for all. One common cause is a heart condition known as atrial fibrillation. NINDS researchers have now found that for most people with this condition, who are under 75 years old, the common drug aspirin provides adequate protection with minimal risk. This finding is important because the alternative to aspirin is a more expensive drug with greater risk for complications. In other ongoing research we are sponsoring a clinical trial to determine whether the hormone estrogen can prevent stroke in post menopausal women. Widespread application of treatments based on all of these findings has the potential to save thousands of Americans from stroke and disability.

NINDS research has also made a difference in the treatment of the youngest Americans affected by brain disorders--very low birthweight infants. These children are usually born prematurely and weigh less than three pounds. Under these conditions the brain is especially at risk for bleeding, which in severe cases can lead to permanent damage. Last year results from a clinical trial demonstrated that a common medication, indomethacin, given 6-12 hours after birth of these infants, dramatically reduced the extent and severity of bleeding, thus reducing the incidence of life-long disability. Very low birthweight babies are also at risk for cerebral palsy. In fact, although they constitute only a small fraction of all births, very low birthweight infants contribute nearly one-third of all cases of cerebral palsy. An NINDS scientist has recently found evidence suggesting that a very common and inexpensive chemical, magnesium sulfate, given to the mothers of these infants before delivery, can almost completely reduce their risk of cerebral palsy.

Modern medical science is often accused of fostering high-technology solutions to health care, and indeed, by its very success, of increasing the cost of medical care. Our ability to improve the survival of those with stroke, with brain or spinal cord injury, or of preterm infants, for example, can be argued to have increased the number of those with expensive disabilities. I would contend, however, that this is to take the short view. In each of the examples described above, stroke and low birthweight infants, a common, simple medication can prevent disease leading to long-lasting disability when applied in situations of risk. As our knowledge increases, we can look forward to more instances in which patients not only survive, but go on to live healthy, independent, and productive lives.

Let me now turn to two areas that are not immediately connected to patient care, but offer great promise for future progress.

Neurogenetics. As you will hear from my colleague, Dr. Francis Collins of the National Center for Human Genome Research, one of the marvels of our scientific age is the ability to find and identify defective genes that are responsible for particular diseases. Interestingly, a large number of genetic diseases affect the brain or neuromuscular system: Huntington's disease, ALS, neurofibromatosis, spinocerebellar ataxia, familial Alzheimer's disease, muscular dystrophy, some types of epilepsy, to name but a few. In many of these cases, the gene has been identified. Yet finding the gene is only the first step in understanding a disease and devising suitable therapies for it. For example, one of the most exciting recent advances in neurogenetics is the discovery that a similar type of genetic defect, a "trinucleotide repeat," is found in several different neurological diseases--fragile X syndrome, myotonic dystrophy, spinobulbar muscular atrophy, Huntington's disease, and several others. In each case, a tiny portion of genetic material is repeated over and over. In Huntington's disease the pattern is repeated 37-100 times, compared to 6-34 times in those who are unaffected. Why this expanded repeat causes disease is completely unknown; the effect appears to be a subtle one, as in several of these cases the diseased gene is "dominant" over the normal gene.

As you can see from this example, even when a defective gene is discovered, much remains to be done to understand how the defect leads to disease. This work is important because gene replacement therapy will not be effective or feasible in many cases. What is needed are therapeutic agents that can intervene in the processes that have gone awry because of the defective gene. One of the powerful ways in which molecular genetics can be used is to create animal models of disease in which to study the pathological process and agents that may modify it. For example, NINDS-supported scientists found in 1993 that a gene responsible for many cases of ALS encodes an enzyme that removes the deleterious by-products of cellular metabolism. This discovery has now led to the production of a mouse that has the same enzyme mutation as is found in the human disease. Agents that can protect against these harmful by-products can now be tested in the mouse model of the disease. Among the agents that can be tested are powerful growth factors recently discovered by researchers. Growth factors have recently been found that appear to protect neurons that degenerate in Parkinson's disease and protect from injury the specific neurons afflicted in ALS--the neurons that control our muscles.

One example in which enzyme replacement therapy has been successful is Gaucher's disease, a genetic disease affecting young children. In this disease, an enzyme that degrades a special class of fat molecules is missing, leading to lipid accumulation. Several years ago NINDS scientists reported success in treating Gaucher's patients by replacing the enzyme. Other scientists are using genetics to attack a different kind of problem, introducing genes or proteins that can be targeted to brain tumors and that will attack them. In all of these cases, a particular problem for the brain is that to introduce large molecules as therapeutic agents it is necessary to breach the cellular wall around the blood vessels--the so-called blood brain barrier that protects the brain. Further research is needed to develop and test the techniques that will allow us to translate advances in genetic knowledge into practical, effective therapies and preventive measures.

Life and death of nerve cells. In many brain diseases--Alzheimer's, Parkinson's, Huntington's, ALS--selected populations of nerve cells die for unknown reasons. In other disorders, cells that are deprived of oxygen die, as in stroke, or damaged cells die, as in traumatic brain or spinal cord injury. In the latter cases, in which large numbers of cells are injured at the same time, we know that the injured and dying cells release chemicals that result in later waves of cell death and injury. Unlike other organs such as the liver, that can regenerate new cells, cell death in the nervous system represents permanent loss, as new nerve cells cannot arise by cell division in the adult. In each of these cases, why do the cells die, and what can we do to prevent this? Recent research tells us that nerve cells are not necessarily just passive victims--in some cases, we know that they can fight back to prevent death, and in others we know that they can activate cellular suicide programs to kill themselves. We also know that external factors, secreted by other cells, can influence whether a cell lives or dies. Thus, to some extent at least, neurons can regulate their survival and that of other neighboring cells. These cellular processes, used by neurons during development and adult life, represent potentially powerful aids to therapy. If we know more about how they work, we could help damaged neurons to help themselves--by therapeutically enhancing their restorative processes and suppressing the processes responsible for death. Thus, one day we hope to be able to delay the progression of stroke or trauma to the nervous system, and to restore the function of nerve cells that have been lost. Much work remains to reach that point, but our progress over the last twenty years has been remarkable and leads us to hope that neurological disease will indeed become the arena for therapy and recovery that we hope for.

Mr. Chairman, the FY 1996 budget request for this Institute is $648,255,000. I would be pleased to answer any questions you might have.

Zach W. Hall, Ph.D.
Director, National Institute of Neurological Disorders and Stroke

EDUCATION:

B.A., Yale University, 1958; Emory School of Medicine, Emory University, 1958-1960; Department of Physiology, Emory University, 1960-1961; Ph.D., Biochemistry (Medical Sciences), Harvard University, 1966.

PROFESSIONAL HISTORY:

Director, National Institute of Neurological Disorders and Stroke, 1994 to present; Head, Biomedical Sciences Graduate Program, University of California, San Francisco, 1992-1994; Jack and DeLoris Lange Professor of Physiology, University of California, San Francisco, 1992-1994; Chairman, Department of Physiology, University of California, San Francisco, 1987-1994; Head, Division of Neurobiology and Neuroscience Graduate Program, 1976-1988; Professor of Physiology, University of California, San Francisco, 1976-1994; Associate Professor, Harvard Medical School, Department of Neurobiology, 1972-1976; Assistant Professor, Harvard Medical School, Department of Neurobiology, 1968-1972; Fellow in Biochemistry, Stanford University, School of Medicine; 1966-1968.

PROFESSIONAL ORGANIZATIONS:

American Association for the Advancement of Science; American Society of Biological Chemists; American Society for Cell Biology; Society for Neuroscience; American Physiological Society; Society for General Physiologists; Editorial Board, Neuron; Fachbeirat (Advisory Coimmittee) Max-Planck Institute für experimentelle Medizin, Göttingen, 1994; Dana Foundation Alliance for the Decade of the Brain Initiative, 1992; Invited Speaker, Government-University-Industry Research Roundtable, National Academy of Sciences, 1989; Nominating Committee, Society for Neuroscience, 1986; Scientific Advisory Committee for Neurobiology, Howard Hughes Medical Institute, 1992 to present; Graduate Fellowship Committee, Muscular Dystrophy Association, 1974-1982.

HONORS, AWARDS, FELLOWSHIPS:

Grass Lecturer, University of Miami, 1995; George Bishop Lecturer, Department of Neurology, Washington University, 1995; Grass Lecturer, University of Wisconsin, Milwaukee, 1994; Fellow, American Academy of Arts and Sciences, elected 1994; Alexander Forbes Lecturer, Grass Foundation, Marine Biological Laboratory, Woods Hole, Massachusetts, 1994; Jacob Javits Investigator in Neuroscience, 1993-1994; Steven Schuetze Lecturer, Columbia University, 1993; Lowell O. Randall Lecturer, Department of Pharmacology, University of Pennsylvania, 1991; Dunaway-Burnham Lecturer, Dartmouth Medical School, 1991; Grass Lecturer, SUNY, Albany, New York, 1984; Jacob Javits Investigator in Neuroscience, 1984-1991; Louis B. Flexner Lecturer, Institute for Neurological Sciences, University of Pennsylvania, 1984; William Evans Visiting Fellow, University of Otago, New Zealand, 1983; Grass Lecturer, University of North Carolina, 1978; Research Career Development Award, National Institute of Neurological Diseases and Stroke, 1972-1976; Fellow of the Medical Foundation, Inc., 1968-1970; Grass Foundation Fellow, Summer, 1961.

Mr. PORTER [resuming]. Dr. Hall, thank you very much for your good testimony. I apologize that I had to not only go down to the floor for a vote, but I also had to go next door to testify before another subcommittee myself, and was not here for your entire statement.

I note, of course, this is your first appearance before the subcommittee. I also note that you've come from the University of California at San Francisco. Dr. Varmus is keeping Nancy Pelosi very happy, certainly.

Dr. VARMUS. As best I can. [Laughter.]

Mr. PORTER. We welcome you and look forward to working together with you.

Dr. HALL. Thank you.

BRAIN IMAGING

Mr. PORTER. When Members of the subcommittee visited NIH in January, we saw some impressive demonstrations of imaging technologies at the clinical center. Are improved brain imaging techniques central to understanding brain diseases, and what new imaging technologies are on the horizon?

Dr. HALL. Yes, brain imaging techniques have proved to be enormously useful. As you know, the brain is encased in the skull. It is difficult to see, to approach, to understand. And the processes that are now in place give us a remarkable ability to look at not only the structure of the brain, but also the functioning brain.

What I mean by that is that as the members of your subcommittee saw when they visited, it's possible not only to outline the major cavities of the brain and the major structures of the brain, so that one can see, for example, brain tumors as they press on nervous tissue or gross deformations of the brain, but using modern techniques one can now actually measure the relative activities of nerve cells during the performance of various tasks, even mental tasks, such as thinking of particular things. One can actually see which areas of the brain are active.

We see these pictures almost daily now in the paper. There's much attention given now to differences of how the brains of men and the brains of women may differ when they perform particular tasks. It is remarkable what one can observe.

In terms of disease, this technology has been very important. An example from our intramural research program is that of multiple sclerosis, where we have a very active group that has used modern techniques of imaging to detect changes in the brain before there are clinical symptoms that are evident. This has proved to be a very powerful diagnostic tool in the early stages of multiple sclerosis. As you know, the symptoms wax and wane during the so-called remitting, relapsing phase of the disease in which people may have difficulty during one week and after a period of time they appear to be just fine. So the question is, do they have multiple sclerosis or do they have something else. It is then very powerful to be able to use these techniques to detect degenerative changes in the brain that one would otherwise not be able to see, and then to diagnose these people as having multiple sclerosis.

It's also a terrific boon as one tests therapies. As you may know, there is a large clinical trial of beta interferon that's going on, and another that's just been completed that offers some hope in multiple sclerosis. One of the major features of these trials was the ability to use these imaging techniques to determine whether the progress of these lesions was retarded or not by the particular drug.

DUCHENNE MUSCULAR DYSTROPHY

Mr. PORTER. We've been approached by some parent groups who are very concerned about Duchenne muscular dystrophy. Can you describe this disease and the number of children it afflicts, and tell us what work is being done in this area at your Institute?

Dr. HALL. Yes. Duchenne muscular dystrophy is an x-linked genetic disease that occurs in about one of every 3,500 male births. Our Institute is very proud to have sponsored the work that resulted in the isolation of the defective gene for Duchenne's muscular dystrophy. The gene turns out to be unusual in that it is a very large one. It occupies a special place in biomedical science, because it was one of the first genes of a major medical disease to be identified.

The gene encodes a protein called dystrophin. Research sponsored by our Institute and others has shown that this protein is found near the surface membrane of muscle cells, where it appears to serve a structural role as part of a complex that links the cytoskeleton of the inside of the cell to structures on the outside of the cell, thus providing mechanical strength. In patients with Duchenne muscular dystrophy, this protein is not made. The cell surface, the membrane, the sheath around the cell is therefore weak and easily damaged. Muscle fibers then die, resulting in muscle weakness.

We continue to have an interest in muscular dystrophy. Our Institute put out a program announcement just last year for gene therapy in Duchenne muscular dystrophy. We anticipate grant applications in response to that program announcement.

We presently support a number of laboratories, including those of the two discoverers of the gene, Lou Kunkel and Eric Hoffman, who continue to work on dystrophin. We support a young clinical investigator at Baylor who is investigating the use of gene therapy for this disease.

I might add as a personal note that the same complex of proteins is important for the formation of synapses, the connection between nerves and muscles. Dystrophin is important not only for the entire muscle surface but also for the specialized contact between nerve and muscle that occurs at synapses. My own lab and others have investigated these processes.

PARKINSON'S DISEASE

Mr. PORTER. Dr. Hall, Congress has urged your Institute to increase your efforts in Parkinson's disease. In fact, I might say the Chairman of the Appropriations Committee, just within the last couple of hours, mentioned Parkinson's disease when we had a meeting earlier today.

In the past, there had been a feeling among outside groups that the research efforts for this disease were not very focused, and that the various Institutes involved needed to increase their cooperative efforts. Which other Institutes fund Parkinson's disease research besides NINDS, and is there one focal point for Parkinson's efforts within your Institute? Finally, last year Congress asked you to hold a consensus conference on Parkinson's. Where does that effort stand?

Dr. HALL. I'm pleased to answer your question—in fact we support a broad effort in Parkinson's disease, both in our intramural program and our extramural program. I would be happy to tell you about that. But first let me answer your question. Our Institute, the National Institute of Mental Health, the Aging Institute and Environmental Health all have efforts in Parkinson's disease. We have several mechanisms for coordinating those efforts. First of all, our program staff are in contact about the work going on in the different Institutes.

I might add that Parkinson's is in an interesting time right now, with considerable progress in the field. There are numerous meetings, both in this country and abroad. Those in the field are very much in touch, and any serious scientist knows what's going on in Parkinson's research, no matter who supports it.

We are planning a conference for this summer that will be organized by Dr. Tom Chase, an NINDS intramural scientist, whose group has been active in Parkinson's for many years. We are working with the Aging Institute, Environmental Health and Mental Health to put on that conference.

BATTEN DISEASE

Mr. PORTER. We heard from public witnesses earlier this year heartwrenching testimony from the parents of children with Batten disease.

Dr. HALL. Yes.

Mr. PORTER. We know that you are trying to increase the research activity in this area. Can you give us your assessment of the scientific potential in Batten research, and is there any hopeful word for these parents?

Dr. HALL. There absolutely is. We have made definite progress in it. Batten disease is a very confusing disease, which arises from a defect in one or more enzymes that causes the accumulation of various materials in cells. Some of these materials are highly fluorescent, leading to the original identification of this disease and the realization that there is a group of diseases here with common characteristics.

There then followed a rather confusing time of research in which people have tried to look at these accumulated products and to infer what the defect is. This has proved to be problematic. But recently, neurogenetic methods have indicated that there are four different genes that can cause Batten disease.

One gene has been localized to chromosome 16. I think that we will soon have very good news with respect to the cloning of that gene. My understanding is that the work is going extremely well, and so we're quite hopeful about it. Identification of the gene will immediately tell us what the defect is, and that will be a major boon.

There has also been other progress. We now know that a novel class of compounds called saposins accumulates in the form of the disease. These proteins are required for the breakdown of sphingolipids. Exactly how that result fits into the picture, we don't know. However, it serves to distinguish this form of disease from other forms which accumulate a subunit of a mitochondrial atpase.

So the biochemistry is in the course of being sorted out. The genetics, is very promising, in that we now realize that there are at least four different genes involved. So I am much encouraged by progress in this area, and I think we will soon have something substantial to report.

Mr. PORTER. That's good news indeed. Thank you, Dr. Hall.

Mr. Stokes.

ASPIRIN AND STROKE

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Hall. Doctor, I was intrigued by your testimony this afternoon relative to the properties in aspirin that are effective in the treatment and prevention of stroke. Can we just talk a little bit about that? Tell us exactly what is occurring with the usage of aspirin in this respect.

Dr. HALL. Well, aspirin can be thought of as a blood thinner, that is, it decreases the clotting activity in the blood. I don't know if you take aspirin on a regular basis or have done so, but if you do and you have cut yourself shaving, you would have noticed that it takes longer for that cut on your face to stop bleeding if you're taking aspirin than if you're not.

It's one of those homely, daily observations that's quite striking once you're aware of it. Aspirin operates exactly the same way in preventing stroke. As you know, there are two kinds of strokes, one in which a clot forms and obstructs the blood vessel, and another in which the blood vessel actually breaks and there's a hemorrhage in the brain.

What aspirin does is to decrease the inherent ability of the blood to clot. This is obviously a dangerous procedure, in that if you decrease blood clotting too much, then you will have spontaneous bleeding, or if you cut yourself seriously, you would bleed to death. It turns out that low dose aspirin is quite safe in this respect. One can take small amounts of it, and this gives substantial protection against the possibility of stroke.

We now have several clinical trials going on with respect to aspirin. The one that I mentioned in my opening remarks had to do with the comparison of the effects of aspirin and a compound called Warfarin, which is also a blood thinner. Warfarin is much more expensive, and it carries a greater risk, in that the danger of overdosage is much greater there. So patients on Warfarin have to come in from time to time to have their clotting time checked, to be sure the dose is just right, and that they're not getting too much. This doesn't seem to be as much of a problem with aspirin.

NINDS sponsored scientists are continuing to investigate now the effects of aspirin in high-risk patients to determine if a combination of a low dose of Warfarin and aspirin may prove to be better for those patients than standard Warfarin therapy.

Mr. STOKES. How well disseminated is this information to the general public?

Dr. HALL. We have an information office that produces publications on stroke, and makes them available to the public, as well as to physicians and to professional societies. However, it is a problem to get this information out to the general public. I might tell you of a study that we are preparing to fund in Chicago, that will actually look at the effects of stroke on an African American population. The point of this study will be to compare aspirin and ticlopidine. Preliminary data indicate that these may be particularly effective in the African American population.

That study will be carried out through community organizations, that is, churches and institutions in the community are being used to recruit people to participate in the study. This is also a potentially powerful way of also disseminating the information to the public about the results that we get.

Let me add that we also have publications in Spanish for members of the Hispanic community.

STROKE IN AFRICAN AMERICANS AND HISPANICS

Mr. STOKES. I'm glad you mentioned that area. My next question was going to deal with the fact that stroke is now the third leading cause of death in the United States, and it is also now the leading cause of permanent disability.

Dr. HALL. That's right.

Mr. STOKES. It is also a major contributor to late-life dementia, is that correct?

Dr. HALL. Yes.

Mr. STOKES. And further, African Americans, if I understand correctly, have more than a 60 percent greater risk of death and disability from stroke than white Americans, is that correct?

Dr. HALL. That's correct.

Mr. STOKES. In addition to the initiative you've mentioned in Chicago, are there other initiatives going on in this area?

Dr. HALL. Indeed there are. Let me make a couple of general points first. Stroke is an enormous problem in our society. There has been a general decrease over the last 20 years due to better control of risk factors, such as smoking, hypertension, high cholesterol levels and so forth.

However, another risk factor for stroke is age. As you indicate, as our population ages, we become more and more at risk for stroke, so that as the population ages we can expect the incidence of stroke figures to increase.

Also, as you indicate, stroke is a severe problem for the African American community. The incidence of stroke is higher; the injury resulting from stroke is more severe; and the death rate from stroke is higher. We have several initiatives aimed at trying to understand the factors that are involved.

A major emphasis in the past has been to isolate and define the factors that increase the risk for stroke. I've mentioned several of them: age, hypertension, diabetes, smoking. And so one question is, are the same risk factors operating in the African American community and in the Hispanic community, or are there separate risk factors that are associated specifically with race.

We have several studies that address those specific questions. One in New York City is looking at the incidence of various kinds of stroke in African American, Hispanic and white populations, comparing these, and comparing the risk factors in each population. One finding that they have made already is that for one particular kind of stroke, involving a clot in arteries within the brain, that is, cerebral atherosclerosis, there is indeed a higher incidence for both African American and Hispanic populations. That higher incidence is explained almost entirely by known risk factors, in particular a higher incidence of diabetes (which I know you discussed with Dr. Kupfer) and the higher incidence of hypertension and high blood cholesterol level.

We have another study in Cincinnati where the intention is to look at every stroke patient at a group of hospitals in the city over a two year period. It's estimated that there will be about a thousand such patients that will be examined, and some 12 percent of those are estimated to be African American. Thus there will be a clear cohort of African Americans in that study.

Mr. STOKES. Thank you very much for that information Dr. Hall.

Mr. Bonilla, I yield to you.

GENDER DIFFERENCES IN THE BRAIN

Mr. BONILLA [presiding]. Thank you, Mr. Stokes.

Dr. Hall, this may not be in your area, but it got my curiosity aroused the other day, because I was watching a documentary on the study of the brain in terms of the differences and what areas are stimulated between men and women. And it was controversial, because there are some who say you shouldn't try to distinguish. But the reality is that we are different.

Dr. HALL. Yes.

Mr. BONILLA. And apparently, there have been extensive studies now that show that very different parts are activated when a thought process is presented. The difference is there.

Are you involved in this at all, and what is your assessment of this research?

Dr. HALL. There has been interest for some time in the idea that the brains of men and women have subtle but definite structural differences between them. These are not large differences. It is not true, for example, that you could look at a brain and say, aha, this brain came from a man or this brain came from a woman.

But if you look very carefully and quantitatively, there are areas of the brain in which you can consistently see a slightly larger area for men and a slightly smaller area for women. There has been much interest in the last several years in looking at these questions. One important question is to understand how these differences arise. We know that there are interactions between the hormonal systems and the brain during development, and that these may be important in determining differences.

The imaging techniques that I talked about earlier in answer to Mr. Porter's question have also been used as you indicate now to look at a number of tasks that people perform, and to say, are the same areas of the brain active or not. There have been some differences reported. Again, the differences are small, but they appear to be statistically significant. I think they tell us, it's not surprising that there would be such differences.

Some of these have received quite a lot of publicity. One I noted claimed that—I can't exactly remember the details of it—but somehow men and women were asked to decide when looking at pictures of other men and women whether they were happy or they were sad. It turns out the women were slightly better at judging this than men.

Mr. BONILLA. There's a medical benefit to this kind of research, is there not?

Dr. HALL. It certainly is important to know those differences in understanding and treating brain disease. We know, for example that there a number of neurological diseases in which there is a difference between the genders. Multiple sclerosis, migraine, are more common in women, for example, than in men. One important question is, what is the basis of these differences and why do they exist. It also may be that the same treatments will not always be appropriate for men and women, so these become important questions from a neurological point of view.

DECADE OF THE BRAIN

Mr. BONILLA. How does NINDS coordinate with the National Institute of Mental Health in doing research involving the Decade of the Brain? Dr. Varmus mentioned it a moment ago.

Dr. HALL. Yes.

Mr. BONILLA. Are both Institutes working as one on a lot of research projects?

Dr. HALL. Yes. Let me say that interest in the brain is now quite widespread at NIH among the different Institutes. Our Institute funds about 30 percent of the total brain research that goes on, which is the largest contribution of any of the Institutes. But Mental Health, Aging, Drug Abuse, as you heard from Dr. Leshner yesterday, Alcoholism, Child Health and Human Development, Heart Lung and Blood, all of these have some component of their research program that concerns the brain.

The different Institutes have tried to be in touch and to coordinate brain research where we can. We have also been working together in order to sponsor research, both in the external community and within the NIH.

One of the things that we do, for example, is to sponsor common program announcements. We are just sponsoring a program announcement, for example with the National Institute of Mental Health that will look at the mechanism by which the AIDS virus gets into the brain, via the blood brain barrier, or in spite of the blood brain barrier, I should say. This is a topic of interest to both Institutes, and so we put out a joint program announcement, saying that we're both interested in this.

And we hope to work together more and more, so that for grantees in the external world, who are concerned with research of common interest, it shouldn't be a major question as to which Institute they go to, but that we could work together smoothly and productively to support the work that we both have a common interest in.

As I'm fond of saying, it's the same brain that we're all interested in, relevant for mental disease, for neurological disease, for developmental diseases of childhood, for aging, for drug addiction, alcoholism. There is a large body of knowledge that we all have a very strong interest in obtaining.

STROKE IN HIS PANICS

Mr. BONILLA. In the past, Dr. Hall, I've asked about Hispanics and the high incidence of strokes among Hispanics.

Dr. HALL. Yes.

Mr. BONILLA. NINDS has told me that the Institute was exploring a lead in the Hispanic population, namely, when Hispanics are admitted to the hospital, within the first six hours of occurrence, if you could lower the blood sugar, you might be able to protect the brain. I understand that the study is currently going on, so if you would, I'd appreciate—if you would tell me what is the status of this study, and do we have any results, even preliminary results, yet?

Dr. HALL. I don't know the status of that study. We have over 1,800 grants, and in the six months that I've been there, I simply don't know all of them. I would be happy to find that out and provide it for the record.

Mr. BONILLA. I'd appreciate that, Dr. Hall.

[The information follows:]

STROKE IN HISPANICS

Thank you for the opportunity to clarify and update information on research activities regarding the role of diabetes as a stroke risk factor for Hispanics. This work is part of a larger research effort to increase the understanding of risk factors, gender, and ethnicity in stroke.

The prevalence of risk factors can differ among population groups. For example, among those who have a stroke, there is a significantly increased incidence of diabetes in Hispanics compared to blacks and whites. More Hispanics have a high level of blood glucose on admission for stroke. This is important to know because a high level of blood glucose immediately after a stroke predicts a greater likelihood of death and disability.

The impact of different types of stroke also can vary among populations groups. A recent finding shows that stroke due to intracranial atherosclerosis was more frequent in blacks and Hispanics. Furthermore, compared with other risk factors, diabetes is important in predicting the presence of intracranial atherosclerosis.

Because of research findings, an NINDS grantee is initiating a community stroke intervention program to disseminate information about stroke and facilitate stroke risk factor modification for high risk individuals. Part of this effort will include efforts to detect and treat diabetes in Hispanics and other ethnic groups.

Dr. HALL. I could just add that we are very concerned with the problem of stroke in the Hispanic community. In my testimony to Mr. Stokes, I mentioned several studies in which we have separate Hispanic, African American and Caucasian cohorts in which we examine the risk factors for strokes.

There are several other things going on that are of particular significance for the Hispanic community. We have in New Mexico a study, for example, with Native American, Hispanic and white cohort, in which the incidence of stroke and the risk for stroke are being compared. We are also carrying out several other studies of significance, importance, and special relevance to the Hispanic community.

In San Francisco, for example, there is an ongoing study looking at the effects of cocaine withdrawal on the development of very young infants. These are children born to mothers that are cocaine addicted. After they are born, they have to go through a period of withdrawal, which has the potential of serious effects in the development of the nervous system. There again, we have African-American, white and Hispanic cohorts.

BIRTH DEFECTS

Mr. BONILLA. I'm very interested in birth defects, looking at a different subject now, because they occur in a disproportionate amount along the Texas–Mexico border, and that has received a lot of national attention as well. In your budget justification, you talk about neural tube defects, spina bifida and the Pax–3 gene regarding birth defects. What do you see happening next in this area?

Dr. HALL. I think neurogenetics is going to help us a great deal. Many birth defects are genetic defects in which a particular gene has gone awry. So we have begun to look at these diseases and to determine for a number of them what the problems are. We have recently published a program announcement expressing our interest in neurogenetic defects of infancy and childhood.

Sometimes we find that quite simple things are effective. Folic acid, is a case in which by simply taking this vitamin, pregnant mothers can cause a major reduction in neural tube defects. That's a case in which an inexpensive and easy treatment offers a major effect.

We continue to look at defects like Batten disease, as we had talked earlier, and spina bifida. And I'm hopeful that we will have more instances to report like that of folic acid.

CALCIUM CHANNEL BLOCKERS

Mr. BONILLA. Dr. Hall, is NINDS concerned about a recent study that found that about 6 million Americans may be increasing their risk of heart attack and stroke by 60 percent by taking a class of drugs to lower blood pressure? That report flooded doctors and pharmacists across the country with phone calls, and one Nebraska woman was hospitalized when she stopped taking her medicine.

Can you tell us anything about this report, Dr. Hall, the methodology and the way it was released to the press, and if patients stopped taking their blood pressure medicine, couldn't the incidence of stroke rise dramatically?

Dr. HALL. Yes. I think this was a study sponsored by the Heart, Lung, and Blood Institute, if I'm not mistaken, and so I don't know the details of the study. I think this concerns calcium channel blocking agents. My understanding is that although there is a risk, it's not a major or dramatic risk and patients are advised to see their physicians to obtain information and also to have careful monitoring of their blood pressure.

Mr. BONILLA. Okay. Dr. Hall, that concludes my questions. If I have something that I think of later, I'd appreciate it if you'd respond for the record.

Dr. HALL. I'll be happy to.

Mr. BONILLA. It was good to hear from you today, and we learned a lot from you and every one of the Directors that have been here from NIH, and we appreciate your input very much.

Dr. HALL. Thank you very much, Mr. Bonilla.

Mr. BONILLA. At this time the committee will stand recessed until tomorrow at 10:00 a.m.

[The following question were submitted to be answered for the record:]

FUNDING FOR SPECIFIC DISEASES

Mr. Porter: Identify FY94-96 direct (versus related) spending for the following: Gaucher's disease, Duchenne muscular dystrophy, Alzheimer's disease, Huntington's disease, multiple sclerosis, head injury, stroke, epilepsy, Batten's disease, neurofibromatosis, dystonia, post-polio syndrome, spinal cord injury, narcolepsy, syringomyelia, supranuclear palsy, and Parkinson's disease.

Dr. Hall: The table below displays NINDS funding levels supporting direct research on the specific diseases listed. In addition, NINDS supports research that is related to these disorders, which has the potential to improve medical understanding, prevention, and treatment.

	FY 1994 Actual	FY 1995 Estimate	FY 1996 Estimate
Gaucher's disease	$5,592,000	$5,632,000	$5,868,000
Duchenne muscular dystrophy	2,573,000	2,599,000	2,720,000
Alzheimer's disease	15,263,000	15,753,000	16,254,000
Huntington's disease	5,180,000	5,330,000	5,535,000
Multiple sclerosis	41,162,000	42,240,000	43,614,000
Head injury	34,897,000	35,952,000	37,165,000
Stroke	69,162,000	71,330,000	73,715,000
Epilepsy	49,721,000	51,229,000	52,715,000
Batten disease	3,034,000	3,128,000	3,227,000
Neurofibromatosis	2,700,000	2,774,000	2,885,000
Dystonia	2,292,000	2,341,000	2,430,000
Post-polio syndrome	1,412,000	1,414,000	1,484,000
Spinal cord injury	16,140,000	16,503,000	17,018,000
Narcolepsy	2,289,000	2,356,000	2,449,000
Syringomyelia	425,000	440,000	453,000
Progressive supranuc. palsy	357,000	338,000	301,000
Parkinson's disease	19,122,000	19,586,000	20,391,000

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of research centers supported in FY 95.

Dr. Hall: The NINDS is planning to support 46 Research Centers in FY 1995. They are anticipated to break down by subject area as follows:

Subject Area	Number
Neurological Disorders of Early Life	1
Neurological Disorders of Aging	
Parkinson's	1
Huntington's	1
Alzheimer's Disease	1
Stroke	5
Epilepsy	6
Sleep Disorders	1
Demyelinating or Sclerosing Disorders	
Multiple Sclerosis	3
Amyotrophic Lateral Sclerosis	1
Neuromuscular Function, Normal & Abnormal	
Muscular Dystrophy	1
Other Neuromuscular Disorders	2
Neurological Infectious Disorders	2
Trauma and Injury	
Head and Brain Injury	9
Spinal Cord Injury	3
Neonatal Brain Injury	4
Brain Tumors	5
Total	46

PARKINSON'S DISEASE

Mr. Porter: What was the $19 million in direct Parkinson's disease research funding spent on in 1994?

Dr. Hall: NINDS supports and conducts a broad range of investigations aimed at discovering the cause(s) of Parkinson's disease (PD), developing improved methods of treatment, finding ways to prevent and ultimately cure the disorder, and restoring function to those who have lost it. Extramurally-supported research efforts include work on toxin-induced neurodegeneration, including both environmental and endogenous toxins; genetic predisposition; altered circuitry and neurochemistry of motor systems; and the search for new therapeutic interventions. A surgical procedure, pallidotomy, has been refined and is now being evaluated for the treatment of PD in a clinical trial. NINDS intramural scientists are isolating individual brain receptors for dopamine using molecular genetic techniques, allowing investigators to screen experimental drugs in tissue cultures. New information about the effects of different dopamine receptors has led to new clinical trials. Intramural scientists are working to develop drugs that target specific dopamine receptors, and that avoid the negative side effects of current pharmacotherapy now experienced by many patients. They are also studying a new compound (Ro 40-7592) that blocks the breakdown of dopamine and levodopa, and prolongs relief of symptoms. The following pages list Parkinson's disease projects funded by NINDS in 1994.

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
SZIRAKI, ISTVAN L	NOVEL SITES OF ACTION FOR DEPRENYL IN MPTP PARKINSONISM	U.S. NATIONAL INSTITUTE OF MENTAL HEALTH
FRANZ, ELIZABETH A	MOTOR DYSFUNCTION IN PARKINSON'S DISEASE	UNIVERSITY OF CALIFORNIA BERKELEY
RAYMON, HEATHER K	ENHANCEMENT OF NIGRAL GRAFT SURVIVAL IN THE STRIATUM	UNIVERSITY OF CALIFORNIA SAN DIEGO
SORTWELL, CARYL E	TROPHIC COGRAFT EFFECTS ON MESENCEPHALIC GRAFT VIABILITY	FINCH UNIV OF HLTH SCI/CHICAGO MED SCH
LOMBARDI, WENDY J	INTENTIONAL RETRIEVAL DEFICITS IN PARKINSONS DISEASE	COLUMBIA UNIVERSITY NEW YORK
HARRISON, MADALINE B	CELLULAR LOCALIZATION OF DOPAMINE RECEPTOR SUBTYPES	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
GANCHER, STEPHEN T	ALTERATIONS IN DOPAMINERGIC RESPONSE IN PARKINSONISM	OREGON HEALTH SCIENCES UNIVERSITY
BUCHMAN, ARON S	MOTOR CONTROL AND MOTOR UNIT RECRUITMENT	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
SALTARELLI, MARIO D	MOLECULAR NEUROBIOLOGY OF THE CHOLINE TRANSPORTER	EMORY UNIVERSITY
PRZEDBORSKI, SERGE E	SOD AND NIGRAL NEURON NUMBER--ROLE IN PARKINSONISM	COLUMBIA UNIVERSITY NEW YORK
ZIGMOND, MICHAEL J	NEUROBIOLOGY OF THE INTACT AND DAMAGED BASAL GANGLIA	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
HANSEN, JOHN T	NEURAL AND PARANEURAL GRAFTS IN PARKINSON'S MODELS	UNIVERSITY OF ROCHESTER
GHETTI, BERNARDINO	NEUROLOGY OF THE WEAVER MUTANT	INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS
DE LONG, MAHLON R	BASAL GANGLIA--FUNCTIONAL CIRCUITRY	EMORY UNIVERSITY
HOFFER, BARRY J	BASAL GANGLIA DISORDERS AND NEUROTRANSMITTER FUNCTION	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
GOLDSTEIN, MENEK	BIOGENIC AMINES AND EXTRAPYRAMIDAL DISORDERS	NEW YORK UNIVERSITY
ANDERSON, MARJORIE E	BASAL GANGLIA OUTPUT	UNIVERSITY OF WASHINGTON

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
DE LONG, MAHLON R	MOTOR FUNCTIONS OF THE BASAL GANGLIA	EMORY UNIVERSITY
STELMACH, GEORGE E	PARKINSONIAN DYSFUNCTIONS IN MOVEMENT ORGANIZATION	ARIZONA STATE UNIVERSITY
MOLINOFF, PERRY B	NEUROTRANSMITTER RECEPTORS IN THE BASAL GANGLIA	UNIVERSITY OF PENNSYLVANIA
JOHNSON, RODNEY L	PRO-LEU-GLY-NH2 AND DOPAMINE RECEPTOR MODULATION	UNIVERSITY OF MINNESOTA TWIN CITIES
ROFFLER-TARLOV, SUZANNE K	INHERITED DOPAMINE LOSS	TUFTS UNIVERSITY BOSTON
WILSON, CHARLES J	NEURONAL ORGANIZATION OF BASAL GANGLIA	UNIVERSITY OF TENNESSEE AT MEMPHIS
NUTT, JOHN G	LEVODOPA PHARMACOKINETICS AND PHARMACODYNAMICS	OREGON HEALTH SCIENCES UNIVERSITY
BROWN, LUCY L	FUNCTIONAL NEUROANATOMY OF MOVEMENT DISORDERS	YESHIVA UNIVERSITY
BROWN, LUCY L	FUNCTIONAL NEUROANATOMY OF MOVEMENT DISORDERS	YESHIVA UNIVERSITY

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
BECKER, J B	BRAIN TISSUE TRANSPLANTATION--EUROCHEMICAL STUDIES	UNIVERSITY OF MICHIGAN AT ANN ARBOR
MARSHALL, JOHN F	STRIATAL ORGANIZATION AND DOPAMINE RECEPTOR LOCALIZATION	UNIVERSITY OF CALIFORNIA IRVINE
MELLER, EMANUEL	RECEPTOR RESERVE AT BRAIN NEUROTRANSMITTER RECEPTORS	NEW YORK UNIVERSITY
COLLINS, MICHAEL A	MPTP BETA CARBOLINES AND THE ETIOLOGY OF PARKINSONISM	LOYOLA UNIVERSITY MEDICAL CENTER
SCHNEIDER, JAY S	NEUROBEHAVIORAL PLASTICITY AFTER DOPAMINE SYSTEM DAMAGE	HAHNEMANN UNIVERSITY
BAKAY, ROY A E	CNS GRAFTING FOR PARKINSONISM	EMORY UNIVERSITY
KUNG, HANK F	NEW CNS DOPAMINE RECEPTOR-IMAGING AGENTS	UNIVERSITY OF PENNSYLVANIA
ZAHNISER, NANCY R	RELEASE-MODULATING DOPAMINE AND ADENOSINE RECEPTORS	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
LEONARD, CHRISTOPHER S	SYNAPTIC MODULATION OF MESOPONTINE CHOLINERGIC NEURONS	NEW YORK UNIVERSITY

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
CHARLTON, CLIVEL G	EXCESS BIOLOGICAL METHYLATION AND PARKINSONS DISEASE	MEHARRY MEDICAL COLLEGE
REINER, ANTON J	NEUROPATHOLOGY AND PATHOGENESIS OF HUNTINGTONS DISEASE	UNIVERSITY OF TENNESSEE AT MEMPHIS
CASTAGNOLI, NEAL, JR	METABOLISM AND NEUROTOXICITY STUDIES OF MPTP ANALOGS	VIRGINIA POLYTECHNIC INST AND ST UNIV
CASTAGNOLI, NEAL, JR	METABOLISM AND NEUROTOXICITY STUDIES OF MPTP ANALOGS	VIRGINIA POLYTECHNIC INST AND ST UNIV
HOFFER, BARRY J	COMPLEX I IN PARKINSON'S DISEASE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
WOLFF, JON A	NONVIRAL GENE THERAPY FOR PARKINSON'S DISEASE	UNIVERSITY OF WISCONSIN MADISON
MYTILINEOU, CATHERINE	DOPAMINE NEURON PRECURSORS AND BRAIN TRANSPLANTS	MOUNT SINAI SCHOOL OF MEDICINE
SALAMONE, JOHN D	VACUOUS JAW MOVEMENTS--POSSIBLE PARKINSONISM MODEL	UNIVERSITY OF CONNECTICUT STORRS
CHARLTON, CLIVEL G	PARKINSONISM--A METHYL-DONOR ACTION FOR MPP+	MEHARRY MEDICAL COLLEGE

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
JOHNSON, STEVEN W	EXCITOTOXICITY AND SODIUM PUMP IN DOPAMINE NEURONS	OREGON HEALTH SCIENCES UNIVERSITY
NELSON, LORENE	ENVIRONMENTAL AND GENETIC RISKS FOR PARKINSONS DISEASE	STANFORD UNIVERSITY
DE LONG, MAHLON R	PALLIDOTOMY IN PARKINSONS DISEASE	EMORY UNIVERSITY
PERLMUTTER, JOEL S	NEUROIMAGING OF PARKINSONISM	WASHINGTON UNIVERSITY
FREED, CURT R	EMBRYONIC DOPAMINE CELL IMPLANTS FOR PARKINSONISM	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
IACOVITTI, LORRAINE M	PURIFIED DOPAMINE NEURONS	HAHNEMANN UNIVERSITY
KORDOWER, JEFFREY H	GRAFTS OF GENETICALLY MODIFIED NIGRAL NEURONS FOR PD	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR
STELMACH, GEORGE E	LOCALIZATION OF PARKINSONIAN MICROGRAPHIA	ARIZONA STATE UNIVERSITY
HECKROTH, JOHN A	NEURONAL RESCUE BY EMBRYONIC NEURAL CELL GRAFTS	ST. LOUIS UNIVERSITY

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
SURMEIER, DALTON J	MUSCARINIC AND DOPAMINERGIC CONTROL OF STRIATAL NEURONS	UNIVERSITY OF TENNESSEE AT MEMPHIS
TRIARHOU, LAZAROS C	DOPAMINE NEURON GRAFTS IN GENETIC EXTRAPYRAMIDAL DISEASE	INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS
DUBINSKY, RICHARD M	EARLY DETECTION OF PARKINSONS DISEASE--PILOT STUDY	UNIVERSITY OF KANSAS MEDICAL CENTER
VITEK, JERROLD L	THALAMIC MECHANISMS UNDERLYING PARKINSONIAN SIGNS	EMORY UNIVERSITY
BROWN, W DOUGLAS	DOPAMINERGIC PET AND MOTOR DYSFUNCTION IN PARKINSONISM	UNIVERSITY OF WISCONSIN MADISON
KANG, UN J	CATECHOLAMINE REGULATION IN GENETICALLY MODIFIED GRAFTS	UNIVERSITY OF CHICAGO
FLITTER, WILLIAM D	NRTS AS TREATMENT IN PARKINSONS DISEASE	CENTAUR PHARMACEUTICALS, INC.
TANNER, CAROLINE M	TWIN STUDIES IN PARKINSONS DISEASE	PARKINSON'S INSTITUTE
FEDIO, PAUL	COGNITIVE AND EMOTIONAL PROFILE OF NEUROPSYCHIATRIC DISO	NATIONAL INSTITUTES OF HEALTH, NINDS

	NINDS - FY 1994 Parkinson's Disease Research	
PI	Title	Organization
WALTERS, J R	PHARMACOLOGY AND PHYSIOLOGY OF THE SUBSTANTIA NIGRA AND	NATIONAL INSTITUTES OF HEALTH, NINDS
CHASE, THOMAS N	PHARMACOLOGY, BIOCHEMISTRY AND PHYSIOLOGY OF CENTRAL NEU	NATIONAL INSTITUTES OF HEALTH, NINDS
OLDFIELD, EDWARD H.	TISSUE IMPLANTATION IN PARKINSONIAN MODELS	NATIONAL INSTITUTES OF HEALTH, NINDS
COMMISSIONG, JOHN W	REINNERVATION AND FUNCTIONAL RECOVERY IN SPINAL CORD INJ	NATIONAL INSTITUTES OF HEALTH, NINDS

HUNTINGTON'S DISEASE

Mr. Porter: What further progress has been made in Huntington's disease since the discovery of the gene?

Dr. Hall: The discovery in 1993 that Huntington's disease (HD) was due to a tiny portion of genetic material abnormally repeated on Chromosome 4 ended the intensive search for the gene and started the quest for understanding its mode of action. The duplicated material is known as a triplet repeat. This discovery is part of one of the most exciting advances in neurogenetics research today. That is, the discovery that a similar type of defect--the triplet repeat--can been found in several different neurological disorders.

In the case of HD, the nucleotide sequence C-A-G is repeated. In the past year, some basic characteristics of the unstable CAG repeat have been delineated. Normal chromosomes carry an array of CAG repeats at the HD locus, ranging from 6 to 34 repeat units in length. The distribution of repeat length on HD chromosomes ranges from 37 to more than 100 copies. These expanded triplet repeat stretches are very unstable in HD transmissions but on normal chromosomes are inherited in a stable fashion.

Investigators have found a statistical correlation between the length of the triplet repeat and the age of onset. This relationship is seen most clearly at the extremes of repeat length. Thus, the longest repeats appear in juvenile onset HD. The propensity for large increases in size to occur when the gene is transmitted from the male explains why juvenile HD arises most often in children of affected fathers. Attempts by a number of groups are now being made to determine if repeat length correlates with progression of the disease. The studies in this area are, however, preliminary. Other genetic, neurobiological, or environmental factors may also influence the rate of clinical decline and neuronal degeneration.

Much further research is being done on the nature of the protein product (named Huntington by the investigators who found the abnormal gene) of the HD gene and how this abnormal protein can bring about the neuronal degeneration late in life and the progressive motor and mental deterioration characteristic of the inherited disease.

REVIEW OF NINDS PROGRAMS

Mr. Porter: Dr. Hall, as you have taken over the reins at the Neurology Institute, have you conducted a systematic review of the Institute's programs to see if any changes in priority or approach are warranted?

Dr. Hall: During my seven months with NINDS, I have focused on the following major areas:

Within the intramural program, I have reviewed the mission, current activities, and recent accomplishments of all the laboratories and branches. We have set in place more rigorous procedures for the periodic reviews by the Board of Scientific Counselors and for the identification of individuals for tenure-track status. We have conducted a careful search for a new Scientific Director and have identified an outstanding candidate for that position. Just prior to the hearings we held a retreat to examine the strengths and weaknesses of the intramural program and to begin charting our course for the future. I am particularly pleased that participants in the retreat included outstanding young scientists as well as research leaders within and outside the NINDS, and I look forward to working with our new Scientific Director and staff to reinvigorate this important national resource.

On the extramural side, we have reviewed and refined the process by which NINDS staff and advisors select projects to be funded beyond the automatic priority-score cutoff. As opportunities arise, I have made a special effort to make sure we recruit promising new science administrators for our extramural program. Together with the National Advisory Neurological Disorders and Stroke Council, we plan a number of important program reviews over the next year, focusing on the various research funding mechanisms; on our funding of clinical trials, and on the training of young scientists.

Keeping in mind that the science we support is of paramount importance, I have consulted with colleagues at the NIH and in the external community about opportunities and needs in the neurological sciences. I have found the interactions with patient groups particularly helpful. I look forward to additional discussions with public and professional groups and with my colleagues at NIH as we seek to identify the areas of highest priority for future efforts.

COLLABORATIVE EFFORTS IN BRAIN RESEARCH

Mr. Porter: Are you encouraging any new approaches or initiatives in brain research conducted across the NIH? Are there better ways to link your research portfolio to those of the Aging and Mental Health Institutes?

Dr. Hall: NINDS will participate in the initiative, "Brain and Brain Disorders" proposed in the budget request. We are also joining with ten other institutes and four other Federal Agencies that support the "Human Brain Project." NINDS has recently initiated or joined in research solicitations dealing with sleep and wakefulness, learning disabilities, and syringomyelia, and we have agreed to join with NIMH in a request for applications for research dealing with HIV and the blood-brain barrier. I have been particularly encouraged by the discussions I have had with directors of NIA, NIMH, and other Institutes concerned with brain research, both individually and as a group, and by their willingness to consider additional areas in which we might collaborate.

NEW TREATMENTS FOR PARKINSON'S DISEASE

Mr. Porter: A January article in Science reported several new approaches to Parkinson's disease that would be less dependent on grafts of fetal tissue--for example, the injection of growth factor directly into the brain. Do you think these approaches hold significant promise for Parkinson's research?

Dr. Hall: These approaches should be explored. Fetal implant studies are just one aspect of a broad and varied range of epidemiology, laboratory, and clinical studies to further the understanding and treatment of Parkinson's disease. Related efforts are underway to investigate cell replacement and growth factor strategies in animals and cell culture. A number of notable discoveries have been made, including the first reports of the apparent regeneration of dopamine-producing neurons in primates. Also, a viral gene vector has recently been developed and been used to insert genes into cells in monkeys with MPTP induced parkinsonism. Preliminary data show the incorporation of labelled viral particles into brain cells increased concentrations of dopamine on the side of incorporation. These findings could lead to new investigations on gene therapy for Parkinson's disease.

DUCHENNE MUSCULAR DYSTROPHY

Mr. Porter: Is Duchenne muscular dystrophy a research area that has attracted many investigators?

Dr. Hall: The discovery of the gene responsible for Duchenne muscular dystrophy and Becker muscular dystrophy and the subsequent identification of the gene product, dystrophin, has created numerous scientific opportunities. NINDS supported research includes efforts to characterize dystrophin and related proteins, to improve diagnosis, and to identify causes and characterize other dystrophies and neuromuscular disorders. NINDS also supports a study to investigate a strategy for gene therapy for Duchenne muscular dystrophy. The grantees supported by NINDS are some of the leading scientists in neuromuscular disease research. In addition, other NIH institutes support research in muscular dystrophy as it relates to cell biology and muscle physiology.

Mr. Porter: Do you feel a request for applications on Duchenne muscular dystrophy would be warranted at this point?

Dr. Hall: In 1994, NINDS issued a program announcement to stimulate research on gene therapy of Duchenne muscular dystrophy and a second announcement on neurogenetic disorders of infancy and childhood that included the dystrophies. At this time, a request for applications would not be warranted.

Mr. Porter: Do you have any plans to try to generate more research in this area?

Dr. Hall: Overall in the United States, research activity in Duchenne muscular dystrophy is exciting and active. Important research questions are being addressed that will lead to treatment and prevention discoveries. NINDS has recently taken steps formally and informally to stimulate new investigator-initiated studies in this and other neuromuscular diseases, and will continue to encourage research in this area.

MULTIPLE SCLEROSIS

Mr. Dickey: What recent advancements have been made in the detection, treatment, and prevention of multiple sclerosis?

Dr. Hall: There is no single specific diagnostic test for multiple sclerosis (MS). Magnetic resonance imaging (MRI), especially gadolinium enhanced, is helpful, but many people have MS-like lesions without symptomatic disease. The NINDS intramural program is conducting studies using MRI to examine the natural history of multiple sclerosis during the early mild, relapsing-remitting phases of the disease. These studies have detected that many patients have substantial evidence of disease even during its early, apparently inactive phase. The effect of interferon beta 1b, a recently approved therapy in MS, has now been studied in patients with early mild, relapsing-remitting MS to test its ability to reduce alterations in the blood-brain barrier as measured by MRI. In those studied, all have a dramatic reduction in lesions, with cessation of disease activity, as measured by MRI, for many.

Mr. Dickey: What treatments are currently available for people with multiple sclerosis?

Dr. Hall: Interferon beta 1b is a recently approved therapy for MS. NINDS scientists have now studied this new drug in patients with early mild, relapsing-remitting MS. All patients in the study had a dramatic reduction in lesions, with cessation of disease activity, as measured by MRI, for many. NINDS supports an MS clinical trial involving another form of beta interferon under the direction of Dr. Lawrence Jacobs at the University of Buffalo, with associated centers at the Cleveland Clinic, Portland, Oregon, Georgetown University, and the Walter Reed Medical Center. Initial reports concerning the efficacy of this experimental therapy are encouraging. Another investigational drug, Copolymer 1, has been found to reduce relapse rate, and is being evaluated for the treatment of relapsing remitting multiple sclerosis. A Phase III clinical trial using this drug has recently been completed, and a treatment investigational new drug program is now in progress to make it available to patients experimentally and to collect additional clinical data.

NERVE INJURY

Mr. Dickey: It is my understanding that it is impossible, or very difficult, to regenerate nerve cells after the nerve has been destroyed or damaged. What problems does nerve regeneration pose as you develop treatments to neurological disorders?

Dr. Hall: Regeneration of nerves involves numerous cellular and molecular processes within the injured nerve cells. Among these are inhibition of cell death, synthesis of new proteins, processing of directional signals from the existing environment, and stabilization of the growing fibers. The regenerating nerve depends upon signals from the environment, both to nourish the parent neuron and to guide the progress of the growing nerve. In the peripheral nervous system, regeneration is quite successful. It is clear that the surrounding support cells both nurture and provide mechanical support for the growing axon nerve fiber. Regeneration in the central nervous system is more problematic. The complex interactions of nerve fibers and cells within the brain and spinal cord require that several growth factors, trophic (nurturing) factors, and extracellular support molecules appear at specific stages of development to influence the final structure of the nervous system. If disease or injury affects this complexity, the exact conditions that had provided support for establishing nerve tracts or nuclei cannot be easily duplicated. It is known that the nervous system produces inhibitory substances that keep axons from straying into inappropriate territory. .Antibodies to these factors permit more vigorous outgrowth from injured fibers, but guidance of the fibers to appropriate targets remains an issue. As more and more of the basic molecular and cellular biology of the nervous system is revealed, more strategies to enhance regeneration are provided.

Mr. Dickey: Does brain trauma fall under the purview of NINDS research? If so, what types of research are currently being conducted, what advancements have been made, and what can we expect from further research of brain trauma?

Dr. Hall: NINDS is the lead institute at the NIH for basic and clinical research on brain trauma. Major emphases are placed on the prevention of secondary damage, regeneration and plasticity, and neurorehabilitation. Areas of basic research include the study of programmed cell death, a natural process to eliminate damaged cells that may undermine recovery from the damage of trauma and ischemia (bleeding). The genetic signals for cellular death appear in some cells after brain trauma; interruption of this may allow recovery of damaged nerve cells. Ways to deliver genetic material to the damaged cells are under investigation. Studies of blood flow and metabolism after acute brain trauma have shown the importance of maintaining blood pressure and prevention of hypoxia after injury. Pharmacological studies indicate that the complexity of the injury may require the use of several drugs in combination, or at specific post-injury times, to prevent secondary damage due to natural responses of the nervous system. The NINDS recently sponsored a workshop on the behavioral and cognitive consequences of head trauma in children, and the usefulness of new structural and functional imaging techniques to assess the severity of the initial trauma and to predict long-term consequences. A multicentered clinical trial of hypothermia to treat severe brain injury is supported by NINDS. The study is currently enrolling patients at seven centers throughout the country.

BRAIN IMAGING

Mr. Dickey: Please explain the recent advancements in brain imaging techniques and how those advancements will improve detection and treatment of brain disorders.

Dr. Hall: Imaging techniques continue to advance in two directions: more precision of static imaging, and functional imaging. Magnetic resonance imaging (MRI) has proven very useful in detecting injuries caused by a variety of diseases and trauma that could not be detected by CT scanning. The progress of the injuries over the course of disease can be followed much more precisely, and interventions may be planned at earlier stages of disease progression, often before serious symptoms are manifest. Design of specific techniques of angiography used in conjunction with MRI provide exquisite detail and allow better decisions on treatment or intervention. In addition, better resolution has allowed identification of injuries within white matter, an important feature resulting from trauma, alcoholic degeneration, and multiple sclerosis. Computer programs are under development to allow images to be standardized and shared with other centers and physicians. Positron emission tomography (PET) scanning of injured brains has made a valuable contribution by showing that increased metabolism in specific regions can be more dangerous than decreased metabolism. Early treatment to prevent increased metabolism may decrease secondary damage after trauma, leading to more favorable outcomes for patients.

DECADE OF THE BRAIN

Mr. Stokes: To what extent are research opportunities that were included in the "Decade of the Brain" initiative still viable? What other institutes are involved in this initiative? What opportunities are ready to be explored, and what are the potential benefits for improving the health of the American people?

Dr. Hall: The opportunities identified for the "Decade of the Brain" are very much alive. I am pleased to report that recent progress in areas such as stroke prevention, vision research, mental and addictive disorders, neurogenetics, and prevention of the complications of low birth weight allow us to reevaluate and to refine some of the goals established at the beginning of the decade. Much remains to be done, however, and fortunately, the science continues to progress at a rapid pace.

Virtually every NIH component is contributing to achieving the goals set out for the Decade of the Brain. Total NIH funding is estimated at $2.14 billion for FY 1995; approximately 30 percent of this amount represents NINDS support. Other institutes with a major funding commitment include NEI, NIMH, NICHD, NIA, NIDA, NHLBI, NIAAA, NCI, NIDDK, NIEHS, and NIDR.

While many individual diseases continue to challenge our efforts, virtually every area of neuroscience offers exciting opportunities and hope for improvements in human health. Rapid progress in neurogenetics is accelerating the pace of research that will lead to treatment for diseases as diverse as muscular dystrophy, amyotrophic lateral sclerosis, Batten disease, neurofibromatosis, many developmental disorders of childhood, and Alzheimer's disease.

Molecular techniques provide us with powerful methods of manipulating molecules and cells that can be used for therapy and for generating animal models of disease which can be used to provide new knowledge and to test new therapies. Broad advances in basic research has given us information about ion channels, receptors and growth factors; about the ability of nerve cells to grow and to regenerate; and about the circuits that make up our brains. The development of sophisticated imaging techniques allows us to pinpoint diseased areas of the brain and to examine the activity of the normal brain during speech, learning and movement. New computational and cognitive methods allow us to study the biological basis of learning, memory and simple behaviors.

Other important work on the life and death of nerve cells is producing important and often surprising information about how selected populations of nerve cells are maintained and why they degenerate, with implications for disorders of movement, sensory processing, and cognition, as well as far recovery from trauma, stroke, and exposure to neurotoxins.

STROKE

Mr. Stokes: It has been said that stroke is one of the most costly health problems, how would you respond to this statement and what can you tell us about the incidence, prevalence, and the cost of stroke to the nation? How extensive is this health problem among women and among men, within each gender how extensive is the problem among African Americans, Hispanics, and other minorities?

Dr. Hall: Stroke occurs when the blood supply of the brain is interrupted because of a blockage or bleeding from a blood vessel in the brain. Because brain cells die from the decreased blood flow and the lack of oxygen, stroke can result in death and disability. Stroke affects more than 500,000 Americans each year and is the third leading cause of death (approximately 145,000 deaths each year). Stroke survivors are estimated at approximately 3 million. Estimated cost of stroke exceeds $25 billion due to the expense of medical treatment for stroke; rehabilitation, such as speech therapy and physical therapy; long term care; and lost wages.

Stroke occurs in all age groups, in both sexes, and in all races. African-Americans experience stroke at a higher rate, have more severe strokes, and are twice as likely to die from a stroke as white Americans. Age-adjusted stroke death rates are the same for men and women except in the age group of 85 years and over, but more women die from stroke because women live an average of almost seven years longer than men. There is an increased risk for one type of stroke, subarachnoid hemorrhage, in younger women.

NINDS supports research to understand risk factors for stroke, to characterize the burden of stroke in different populations at risk, including women and minorities, and to evaluate methods of treatment and prevention appropriate to different population groups. For example, NINDS supports research to compare the impact of stroke among Hispanics, whites, and Blacks in a population in New York. One study compares the frequency of strokes in different ethnic groups and the risk factors that they have before a stroke occurred. The other study examines the risk of a second stroke in those who have been hospitalized with stroke. Both studies focus on minority group and gender as risk factors for stroke risk and recurrence. As part of this research, investigators have looked at the importance of race in one type of stroke--known as intracranial atherosclerosis. They found this type of stroke to be more frequent in Blacks and Hispanics. The greater prevalence of diabetes and high cholesterol accounted for much of the increase.

As we learn more from these and other stroke research studies we hope to move further towards improved diagnosis, treatment, and prevention of stroke. For example, NINDS supports a major clinical trial to determine the benefit of estrogen to reduce the risk of death or recurrent stroke in post-menopausal women who have had a recent ischemic attack or non-disabling stroke. NINDS will soon fund a new trial to determine the effectiveness of a medication to prevent stroke in an African-American population. The reason for this trial is that previous studies suggest that African-Americans may have a more favorable response to the medication that will be used in the study than the general population.

Mr. Stokes: What do we lose by not continuing to make new basic science and clinical discoveries that lead to new strategies to prevent and treat stroke?

Dr. Hall: In the 1970s and early 1980s, there was a rapid decline in the incidence of stroke, but recent evidence suggests that decline may have ended. As the population ages there will be more older people at risk for stroke. Therefore, more strokes will be occurring. This could mean an increase in medical care costs. Stroke kills about 20 percent of those stricken; many of those who survive are disabled, often requiring nursing home care and extensive rehabilitation in addition to the initial hospitalization.

New strategies are being explored and brought forward, namely vitamin supplementation, hypothermia, thrombolytic therapy, and neuroprotective agents such as calcium channel blockers, NMDA antagonists, and ICAM antibodies. Discoveries from basic research are vital to continued progress against stroke as well as the wide range of biomedical questions we face today.

The development of strategies to treat and prevent stroke is also focusing on specific populations at risk. There is continuing effort to evaluate those patients with atrial fibrillation, those with previous lacunar infarction, those with lupus antibodies, those with patent foramen ovale, and African Americans with previous TIA or mild stroke.

These strategies and more will be needed to prevent the increase in the number of Americans that suffer prolonged, mind destroying, (and expensive) disability due to stroke.

Mr. Stokes: How much Stroke Research, Research Training, and Outreach will the Presidents Budget allow the Institute to support in FY 1996, and does this compare with the FY 1995 and FY 1994 funding level.

Dr. Hall: In fiscal year 1996, the estimates for the President's budget for the National Institute of Neurological Disorders and Stroke (NINDS) for Stroke Research is $73,715,000. The NINDS estimate that of this total, $266,992 will be spent on Research Training and $33,000 will be spent on outreach programs. The fiscal year 1995 estimate is $71,330,000 with $259,000 for training and $32,000 for outreach programs. The actual amount spent on stroke research in Fiscal Year 1994, was $69,162,000 of which $726,889 was spent on Training Research and $31,000 was spent on outreach programs. The total estimated funding level for Stroke Research in Fiscal Year 1996 is 6.58% over Fiscal Year 1994 actual and 3.34% above Fiscal Year 1995 estimates.

CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and has yielded comparable economic savings as well. What have we learned from the Institute's "stroke prevention" clinical trial, and from the low birth weight trial?

Dr. Hall: NINDS can report advances in medical and surgical methods to prevent stroke. Previously, results of a trial supported by NINDS demonstrated that a surgical procedure (carotid endarterectomy) can reduce the risk of stroke in people who have experienced warning signs and have extensive blockage of the carotid arteries leading to the brain. In 1994, it was announced that endarterectomy of an artery with 60 percent or greater narrowing and without a history of previous transient ischemic attack (TIA) or mild stroke on the same side can prevent stroke or stroke death when performed by surgeons with a very low perioperative complication rate of stroke or death. Without surgery, approximately 10 percent of patients with severe carotid narrowing will have a stroke after five years. With surgery, the stroke rate is reduced to 5 percent over 5 years.

In 1994, NINDS grantees reported the results of the second in a series of clinical trials testing agents for preventing strokes in patients with atrial fibrillation, a heart condition. An earlier trial had established that patients with atrial fibrillation can lower their risk of stroke 50 to 80 percent by taking either aspirin or warfarin. The question remained as to whether aspirin, which is less expensive and less toxic, is as effective as warfarin. Because it is expensive and its use requires constant monitoring, some patients with atrial fibrillation have avoided using warfarin. The most recent clinical trial finding shows that for most people with atrial fibrillation under 75 years old, and for those over 75 with no additional stroke risk factors such as high blood pressure or heart disease, the common drug aspirin provides adequate protection with minimal complications. Thus, the results of this trial may encourage more patients--without risk factors like hypertension or history of heart disease--to take aspirin as a preventive measure to reduce their risk of stroke. The findings from these studies are being confirmed with further clinical research that will establish the durability of the results over time and whether aspirin and warfarin can be combined to yield a greater risk reduction for stroke in those who have risk factors.

An estimated 20 to 40 percent of very low birthweight infants are at risk of bleeding in the brain shortly after delivery, a condition called intraventricular hemorrhage (IVH). The more severe forms of IVH can result in death or life-long neurodevelopmental problems. Results from an NINDS-supported clinical trial show that very low birthweight babies, if treated within 6-12 hours of birth with a drug called indomethacin are less likely to have IVH. The study also showed that when IVH does occur in treated patients, it is less severe, and therefore, less likely to cause extensive brain damage. A major conclusion from the study indicated that treatment should result in decreased morbidity and a better chance for normal outcome. Infants in the trial are being followed to assess their neurodevelopment in the first few years of life.

Mr. Stokes: What other significant trials are underway or planned for implementation in FY 1996? What level of funding is included in the FY 1996 Budget for Clinical Trials? How many trials would be funded? How many of these trials are new and how many are ongoing?

Dr. Hall: New clinical trials under consideration for funding in FY 1996 include the following: Treatment Evaluation in Huntington's Disease; Drug Therapy of Status Epilepticus; Prevention of Intraventricular Hemorrhage; Treatment of Cerebral Palsy with Baclofen; and Intra-arterial TPA for Acute Stroke. The level of funding for FY 1996 for clinical trials will be $41,524,000. This level supports a total of 44 clinical trials, of which 37 are ongoing and 7 are new.

DISSEMINATION OF RESULTS

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously? Is there a specific system in place for disseminating such information?

Dr. Hall: Because of rapid advances in the field of clinical neuroscience, the NINDS has been called upon three times in the past four years to disseminate unexpected clinical trial results with important implications for the public health.

The NINDS has developed an effective and efficient system for getting out such information. As the first step in this process, the Data and Safety Monitoring Board advises the Institute that a trial should be stopped or brought to early conclusion. The study leaders then immediately notify the patients involved in the study of the board's recommendations so that they may choose treatment options. The next step is for the study leaders, working with NINDS scientific and information office staff, to develop a statement summarizing the results for the medical community. This document, called a "Clinical Alert" or "Clinical Advisory," must be carefully drafted and approved by the study's executive committee and independent expert reviewers. The statement is then faxed to the leaders of the appropriate professional organizations who use a variety of mechanisms to alert their membership of the news as quickly as possible. Very shortly after the medical community is notified, the NINDS issues a news release and holds a press conference to alert the public to the research findings. The timing is structured this way so that physicians will be aware of a recommended change in medical practice before their patients start seeking advice. Finally, the NINDS develops materials that can be sent to the public in answer to their questions about the research news.

A recent and successful example of this system took place last September when NINDS announced the early conclusion of its 39 site clinical trial on stroke prevention called the Asymptomatic Carotid Atherosclerosis Study. The safety board reported data showing that patients in the surgical group had a much lower risk of stroke than those who did not get the surgery. Physicians participating in the study notified participating patients on September 16 and 17; NINDS prepared and distributed the clinical advisory on September 19-23, and on September 30 NINDS hosted a major national press briefing announcing the results to the public. Because of the thorough preparation and planning, the public received a clear and understandable message about the stroke surgery finding, allowing them to consult with physicians who had the latest available information needed to advise their patients.

NEURO-AIDS AND CANCER RESEARCH

Mr. Stokes: What is the most significant AIDS research underway at NINDS? To what extent has knowledge gained in AIDS research and breast cancer had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your Institute?

Answer: During the course of HIV infection, a variety of neurological manifestations and syndromes occur in as many as 30-50% of AIDS patients. The symptoms include slowing of movement, reflexes and thought, behavioral and neuropsychiatric dysfunction, and even partial paralysis. The damage to the nervous system is caused by the virus and indirect effects of the patient's own cellular substances excreted in response to HIV invasion. As a result of the immune system failure seen in AIDS, patients may face the additional complication of acquiring opportunistic infections that affect the brain.

The NINDS funds many promising areas of research to address the following important questions:

1. How the HIV virus enters the nervous system through the blood-brain barrier; what factors enhance or deter this phenomenon.

2. How HIV proteins and gene products as well as the body's own cell responses affect nervous system function.
3. Are some strains of the virus more inclined to infect the nervous system?
4. Why do only some AIDS patients experience nervous system abnormalities? How can we predict the course and severity of the nervous system disease?
5. Does the virus act differently in children than in adults?
6. How can we prevent and treat HIV encephalopathy and opportunistic infections of the nervous system?

Mouse and monkey "animal models" of neuro-AIDS are being developed to study viral genetics and to test therapies.

Two other AIDS-like retroviruses (HTLV-I and HTLV-II) that affect the human nervous system were discovered before HIV was identified. Previous research on these viruses gave NINDS an early strong scientific base for conducting HIV research. Conversely, advances in HIV research may aid in understanding the HTLV retroviruses.

The brain is a common area of secondary metastasis of breast cancer, and the NINDS and NCI collaborate on some brain tumor research. Moreover, abnormalities of the P53 gene are associated with breast cancer and brain tumors. While much breast cancer research has little relation to neurological disorders, the NINDS does have an interest in the general problem of factors that regulate cell growth and renewal.

NEUROLOGICAL DISORDERS IN CHILDREN

Mr. Stokes: For children, neurological disorders can mean a lifetime of disability. To what extent are we making advances in preventing neurological disorders in low birthweight infants and in children in general?

Dr. Hall: Neurological disorders in children can result in permanent disability. Recent advances in prevention include the finding from a clinical trial that very low birthweight babies treated within 6-12 hours of birth with a drug called indomethacin lowers the incidence and severity of intraventricular hemorrhage (IVH), and reduces the mortality and morbidity of IVH.

In a second study, an NINDS scientist, in collaboration with the California Birth Defects Monitoring Program, has observed that administration of magnesium sulfate to women before and during preterm delivery is associated with a reduction in the frequency of cerebral palsy in very low birthweight infants born of those deliveries. The magnesium sulfate was provided to the mothers as a therapy to prevent preterm labor or to prevent eclampsia. As very low birthweight infants (weighing less than 3.3 pounds) are much more likely to have disabling cerebral palsy than infants of normal weight, it is important that further research more fully explore this observation which could have an important clinical application.

Results announced in 1993 from an NINDS-supported clinical trial demonstrated that a medication (diazepam taken by mouth) provided during a febrile illness can reduce the recurrence of seizures due to fever in young children.

NINDS has supported research on brain surgery for epilepsy in both children and adults who have severely disabling seizures not effectively controlled by antiepileptic drugs.

Recent studies have shown that the incidence of neural tube defects is decreased in children born to women who supplement their intake of folic acid prior to conception and in the early weeks of pregnancy. One of these studies was funded by NINDS. NINDS staff participated in developing widely publicized U. S. Public Health Service recommendations regarding folate supplementation for women planning to become pregnant.

The NINDS has funded four exploratory neonatal brain disorders research centers and two neonatal seizures research centers. These centers are applying and developing state-of-the-art technologies including neuroimaging and spectroscopy to the study of the neonatal brain. One center is assessing the efficacy in neonates of a neuroprotective agent to prevent brain damage which may occur during surgery to correct life threatening heart defects.

Mr. Stokes: We heard considerable testimony from public witnesses this year concerning brain disorders in children. How extensive is this problem? What opportunities are on the horizon and are ready to be exploited regarding the treatment and prevention of brain disorders in children?

Dr. Hall: Children are at risk for a great number of neurological disorders. Children may be born with cerebral palsy, neural tube defects, effects from maternal drug use, or genetic diseases that affect cognitive and motor development. Infants born prematurely and of very low birthweight are at risk for bleeding in the brain and seizure disorders that may have lasting effects. In the first few years of life, children may be found to have cerebral palsy, motor and mental delays, muscular dystrophy, autism, brain tumors, and many neurogenetic disorders such as Tay-Sachs disease, Batten disease, and tuberous sclerosis. Children are also at risk for head injury and epilepsy, and at school age for learning disabilities and attention deficit syndromes. Many of these pediatric neurological brain disorders produce significant permanent disability without significantly reducing life expectancy. Thus the social and economic costs of these disabilities can persist for many decades. For this reason, research to prevent the development of neurological disorders in children is very cost effective.

As more is learned about the genetic basis of neurological disorders, more effective prevention and/or treatment strategies may be developed. For example, a team of NINDS intramural scientists worked for years to successfully develop enzyme replacement therapy for one type of Gaucher's disease. Subsequent studies have focused on refining the dosage to achieve a therapeutic effect with less enzyme, on applying similar techniques to other disorders, on developing a recombinant enzyme, and on gene therapy. In a large multi-center clinical trial NINDS-funded scientists are assessing the efficacy of early bone marrow transplantation to correct the metabolic defect in neuronal storage diseases before brain damage progresses.

NINDS is also supporting a study designed to determine the threshold of closed head injury which produces significant consequences during the first year post injury in children and adolescents.

Another area of research opportunity is that of correlating specific cognitive defects with abnormal brain structure or function. This strategy, used successfully in studies of Williams syndrome, autism, and Turner syndrome, may be applicable to other cognitive defect syndromes.

In epilepsy, the development of antiepileptic drugs specifically for pediatric use is an important research issue. The NINDS sponsored a workshop on this topic to promote further research.

Part of the NINDS effort to encourage research in neurological disorders of children includes the issuance of solicitations to stimulate research in neurogenetic disorders of childhood, gene therapy for genetic metabolic diseases, diagnostic methods to assess neurologic integrity in the fetus/neonate, learning disabilities, and gene therapy for muscular dystrophy.

SUCCESS RATES

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years?

Dr. Hall: For the National Institute of Neurological Disorders and Stroke (NINDS) the success rate has decreased slightly over the five to ten year period. The success rate for NINDS in FY 1985 was 30.6%; for FY 1989 it was 32.4%; and for FY 1994 it was 26.1%

AVERAGE COSTS

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Hall: The average cost of research project grants in current dollars and in two types of constant dollars, Biomedical Research and Development Price Index (BRDPI) and in Consumer Price Index (CPI) is as follows:

Competing Grant Average Costs
in Current and Constant Dollars
(Dollars in thousands)

1985			1989			1994		
Current	BRDPI	CPI	Current	BRDPI	CPI	Current	BRDPI	CPI
$154	$154	$154	$175	$145	$153	$225	$149	$163

MINORITY AND WOMEN APPLICANTS--SUCCESS RATE

Mr. Stokes: What is the success rate for research applications received from minority researchers?

Dr. Hall: To comply with federal mandates, all questions related to race and gender are identified as optional on all research grant applications. Although statistics vary from year to year, a significant number of grant applicants-25 percent in FY 1994-chose not to identify their race and/or gender. These applications are included in the "unknown" category. Since there is no way to predict accurately the race and/or gender composition of these applicants, NINDS is unable to identify accurately the number of applications submitted by minorities and women or the number of awards made to minorities and women. As a result, the following data may not provide a true representation of NINDS support of minority and women researchers.

FY 1994 Competing Grant
Success Rates for Minority Researchers

Fiscal Year	Asian	African American	Hispanic	Native American	Unknown	White
1994	19.0%	40.0%	13.9%	0.0%	30.2%	25.9%

Mr. Stokes: What is the success rate for research applications received from women?

Dr. Hall: In FY 1994, 332 of the 1,734 grant applicants identified their gender as female. Of these, 77 grants were awarded to women researchers, achieving a success rate of 23.2 percent. Another 1,335 identified their gender as male. Of these, 355 awards were made, achieving a success rate of 26.6 percent. The remaining 67 chose not to answer the optional questions on the grant application related to gender. Of these 20 awards were made to this group achieving a success rate of 29.9 percent.

Mr. Stokes: What is the success rate for research applications received from African Americans?

Dr. Hall: In FY 1994, of the 1,293 grant applicants who chose to answer the optional questions on the grant application related to race, 5 identified themselves as African American. Of these applications 2 grants were awarded, achieving a success rate of 40.0 percent.

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Hall: In FY 1994, none of the 4 applications received from Historically Black Colleges and Universities were funded. The Institute did support a new initiative of $1,000,000 for a Developmental Neuroscience Research Grant. This will establish a Neuroscience Research Center at Morehouse School of Medicine. The Center will bring interested researchers together to interact scientifically, and will train minority science majors in the neurosciences.

MINORITY AND WOMEN APPLICANTS--AVERAGE COSTS

Mr. Stokes: For the same time period, in real and in constant dollars what has been the average costs of research project grants awarded to women?

Dr. Hall: The following data identifies the FY 1994 average cost of competing awards by gender in real and constant dollars. Questions related to race and gender are optional on NINDS grant applications. As a result, the following table identifies a gender category denoted as "unknown" which represents the average cost of competing grants for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NINDS support of women researchers:

FY 1994 Competing Grant Average Costs by Gender
in Current and Constant Dollars
(Dollars in thousands)

	1985			1989			1994		
	Current	BRDPI	CPI	Current	BRDPI	CPI	Current	BRDPI	CPI
Men	$158	$158	$158	$180	$148	$157	$227	$151	$164
Women	134	134	134	153	126	133	211	140	153
Unknown	89	89	89	202	167	176	229	152	166

Mr. Stokes: For the same time period, in real and in constant dollars what has been the average costs of research project grants awarded to minority researchers?

Dr. Hall: The following data identifies the average cost of competing awards to minority researchers in real and constant dollars. Questions related to race are optional on NINDS grant applications. As a result, the following table identifies a category denoted as "unknown" which represents the average cost of competing grants for applications in which ethnicity of the awardee could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NINDS support of minority researchers:

Competing Grant Average Costs for Minority Researchers
in Current and Constant Dollars
In Five Year Increments FY 1985, FY 1989, and FY 1994
(Dollars in thousands)

	1985			1989			1994		
	Current	BRDPI	CPI	Current	BRDPI	CPI	Current	BRDPI	CPI
Minority	$162	$162	$162	$148	$122	$129	$192	$128	$139
White	152	152	152	177	146	127	227	151	164
Unkwn	220	220	220	209	172	150	229	152	166

Mr. Stokes: For the same time period, in real and in constant dollars what has been the average costs of research project grants awarded to African American researchers?

Dr. Hall: The following data identifies the average cost of competing awards to African American researchers in real and constant dollars. Questions related to race are optional on NINDS grant applications. Since there is no way to predict the composition of the applicants in the "unknown" category, the following data may not provide a true representation of NINDS support of African American researchers:

Competing Grant Average Costs for African American Researchers
in Current and Constant Dollars
In Five Year Increments FY 1985, FY 1989, and FY 1994
(Dollars in thousands)

	1985			1989			1994		
	Current	BRDPI	CPI	Current	BRDPI	CPI	Current	BRDPI	CPI
African American	$446	$446	$446	$143	$118	$124	$116	$77	$84

Mr. Stokes: For the same time period, in real and in constant dollars what has been the average costs of research project grants awarded to HBCUs?

Dr. Hall: In FY 1985 the average costs of research project grants to HBCUs was $735,460. In FY 1994 the average cost was $136,000. The Institute supported a new initiative of $1,000,000 for a Developmental Neuroscience Research Grant. This will establish a Neuroscience Research Center at Morehouse School of Medicine. The Center will bring interested researchers together to interact scientifically, and will train minority science majors in the neurosciences.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

FY 1996 Budget | Page No.

Organization chart 48

Appropriation language 49

Amounts available for obligation 51

Budget mechanism table 52

Summary of changes 54

Budget authority by object 56

Administrative costs 58

Significant items in House and Senate Appropriations Committee Reports 59

Authorizing legislation 64

Appropriation history 65

Budget authority by activity 67

Justification:

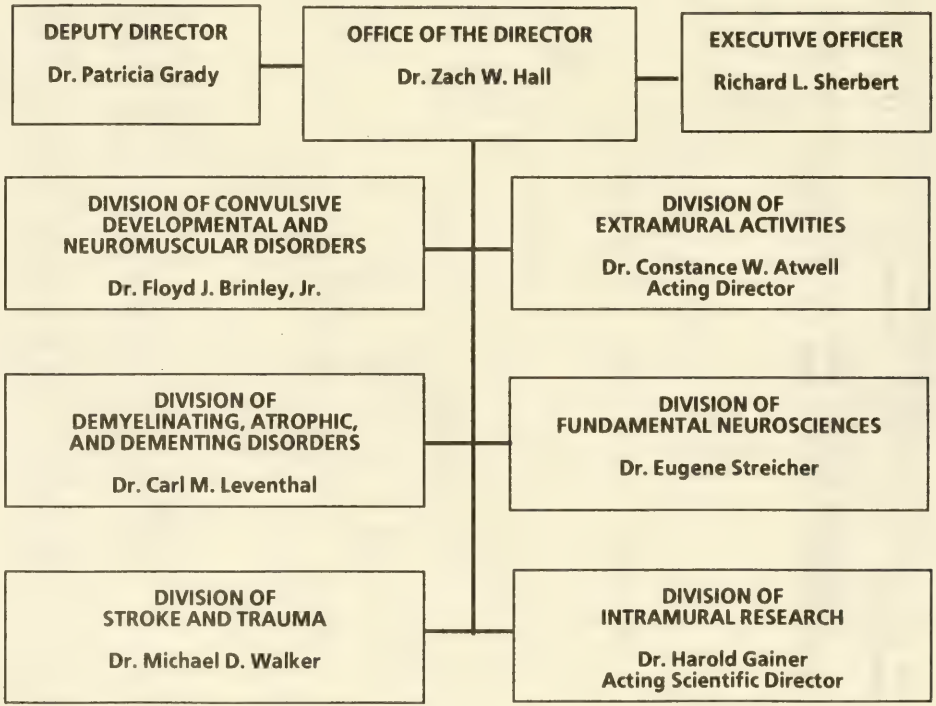
A. General statement 69
B. Extramural research 72
C. Intramural research 81
D. Research management and support 83
E. Detail of full-time equivalent employment (FTE) 84
F. Detail of end-of-year employment 85

48

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Organization Structure


DEPUTY DIRECTOR
Dr. Patricia Grady
OFFICE OF THE DIRECTOR
Dr. Zach W. Hall
EXECUTIVE OFFICER
Richard L. Sherbert
DIVISION OF CONVULSIVE DEVELOPMENTAL AND NEUROMUSCULAR DISORDERS
Dr. Floyd J. Brinley, Jr.
DIVISION OF EXTRAMURAL ACTIVITIES
Dr. Constance W. Atwell
Acting Director
DIVISION OF DEMYELINATING, ATROPHIC, AND DEMENTING DISORDERS
Dr. Carl M. Leventhal
DIVISION OF FUNDAMENTAL NEUROSCIENCES
Dr. Eugene Streicher
DIVISION OF STROKE AND TRAUMA
Dr. Michael D. Walker
DIVISION OF INTRAMURAL RESEARCH
Dr. Harold Gainer
Acting Scientific Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, [$628,301,000] *$648,255,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation	$630,650,000	$628,301,000	$648,255,000
Section 205 Procurement reduction	---	-321,000	---
Section 207 Rent reduction	---	-33,000	---
Section 513 S&E reduction	---	-221,000	---
Subtotal, adjusted appropriation	630,650,000	627,726,000	648,255,000
Comparable transfer to: Office of AIDS Research, NIH for HIV Activities	-22,113,000	---	---
Comparative transfer to/from: Other NIH Institutes for Management Fund adjustment	1,817,000	1,737,000	---
Subtotal, adjusted budget authority	610,354,000	629,463,000	648,255,000
Unobligated balance lapsing	-66,000	---	---
Total obligations	610,288,000	629,463,000	648,255,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994 -- $3,035,000; FY 1995 -- $4,400,000 and FY 1996 -- $4,400,000. Excludes $82,000 for Royalties in FY 1994 and $65,308 in FY 1995.

Also excludes funding for HIV activities: FY 1995 -- $22,741,000; FY 1996 -- $23,807,000, included in Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Mechanism

	1994 Actual BA		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting projects...........	1342	$319,387,000	1202	$298,806,000	1333	$334,934,000
Administrative supplementals....	(68)	2,205,000	(68)	2,295,000	(40)	1,763,000
Competing projects:						
Competing renewals............	188	44,391,000	280	68,880,000	196	50,262,000
New.........................	245	51,588,000	251	54,762,000	239	54,474,000
Supplemental..................	4	291,000	5	539,000	4	454,000
Subtotal, competing.........	437	96,270,000	536	124,181,000	439	105,190,000
SBIR/STTR......................	58	7,348,000	72	9,530,000	73	9,994,000
Subtotal, research projects.....	1,837	425,210,000	1,810	434,812,000	1,845	451,881,000
Research Centers:						
Specialized/comprehensive ctrs..	43	34,510,000	46	38,227,000	43	36,611,000
Other Research:						
Research career programs........	214	16,958,000	206	17,301,000	206	17,758,000
Cooperative clinical research...	1	984,000	4	3,355,000	3	2,702,000
Minority Biomedical Support.....		313,000		313,000		320,000
Other research related..........	34	2,718,000	20	1,608,000	20	1,657,000
Subtotal, other research......	249	20,973,000	230	22,577,000	229	22,437,000
Total, research grants..........	2129	480,693,000	2086	495,616,000	2117	510,929,000

Training						
Individual awards						
Noncompeting	65	1,793,000	83	2,416,000	58	1,761,000
Competing	112	2,926,000	85	2,421,000	110	3,293,000
Subtotal, individual	177	4,719,000	168	4,837,000	168	5,054,000
Institutional awards						
Noncompeting	299	7,421,000	270	6,956,000	289	7,696,000
Competing	60	1,621,000	83	2,406,000	64	1,848,000
Subtotal, institutional	359	9,042,000	353	9,362,000	353	9,544,000
Total, training	536	13,761,000	521	14,199,000	521	14,598,000
Research & Development Contracts	57	16,812,000	65	19,856,000	62	19,856,000
SBIR/STTR	(8)	(753,000)	(18)	(1,753,000)	(17)	(1,753,000)
	FTEs		FTEs		FTEs	
Intramural Research	474	73,272,000	486	73,027,000	481	75,351,000
Research Management and Support	195	25,816,000	194	26,765,000	192	27,521,000
Total	669	610,354,000	680	629,463,000	673	648,255,000
Clinical Trials		(38,341,000)		(40,069,000)		(41,524,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Summary of Changes

1995 Estimated budget authority	$629,463,000
1996 Estimated budget authority	648,255,000
Net change	+18,792,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$30,922,000		+$375,000
b. Annualization of Jan. 1995 Locality Pay		30,922,000		+262,000
c. January 1996 pay increases		30,922,000		+562,000
d. Payment for centrally furnished services		28,828,000		+1,304,000
e. Service and supply fund increase		2,287,000		+72,000
f. One more day of pay		30,922,000		+121,000
g. Laboratory supplies, materials and other expenses		13,277,000		+307,000
Subtotal		--		+3,003,000
2. Research Management & Support				
a. Within grade increase		11,668,000		+167,000
b. Annualization of Jan. 1995 Locality Pay		11,668,000		+99,000
c. January 1996 pay increases		11,668,000		+212,000
d. Payment for centrally furnished services		5,750,000		+302,000
e. Service and supply fund increase		1,804,000		+46,000
f. One more day of pay		11,668,000		+46,000
g. DHHS Working Capital Fund		588,000		-94,000
h. FTS		282,000		-57,000
i. Unemployment Compensation and FECF		170,000		+6,000
j. Supplies, materials and other expenses		9,347,000		+222,000
Subtotal		--		+949,000
Subtotal, Built-in		--		+3,952,000

	1995 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting	1,202	301,101,000	+131	+35,596,000
b. Competing	536	124,181,000	-97	-18,991,000
c. SBIR/STIR	72	9,530,000	+1	+464,000
Total	1,810	434,812,000	+35	+17,069,000
2. Research centers	46	38,227,000	-3	-1,616,000
3. Other research	230	22,577,000	-1	-140,000
4. Research training	521	14,199,000	--	+399,000
5. Research and development contracts	65	19,856,000	-3	--
Subtotal, extramural	2,672	529,671,000	+28	+15,712,000
	FTEs		FTEs	
6. Intramural research	(486)	73,027,000	(-5)	-679,000
7. Research management and support	(194)	26,765,000	(-2)	-193,000
Subtotal, Program		--		+14,840,000
Total changes		--		+18,792,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	680	673	-7
Full-time equivalent of overtime and holiday hours	4	4	---
Average ES salary	$108,960	$111,357	+$2,397
Average GM/GS grade	9.9	9.9	---
Average GM/GS salary	$45,314	$47,145	+$1,831
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207) ..	76,907	78,599	+1,692
Average salary of ungraded positions .	25,186	26,204	+1,018
Personnel compensation:			
Full-time permanent	$22,217,000	$22,997,000	+$780,000
Other than full-time permanent	7,828,000	8,117,000	+289,000
Other personnel compensation	1,396,000	1,476,000	+80,000
Special personal services payments .	3,682,000	3,769,000	+87,000
Subtotal, personnel compensation .	35,123,000	36,359,000	+1,236,000
Personnel benefits	7,267,000	7,610,000	+343,000
Benefits for former employees	200,000	50,000	-150,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Travel and transportation of persons .	$995,000	$1,039,000	+44,000
Transportation of things	274,000	283,000	+9,000
Rent, communications and utilities:			
Rental payments to other than GSA ..	6,000	6,000	---
Communications, utilities, and miscellaneous charges	1,679,000	1,673,000	-6,000
Subtotal, rent,communications ..... & utilities	1,685,000	1,679,000	-6,000
Printing and reproduction	432,000	439,000	+7,000
Other services:			
Consulting service	340,000	340,000	---
Other services	10,779,000	10,490,000	-289,000
Purchases from Govt. accounts	34,578,000	36,273,000	+1,695,000
Operation of GOCOs	1,500,000	1,500,000	---
R & D contracts	18,356,000	18,356,000	---
Supplies and materials	5,418,000	5,535,000	+117,000
Equipment	2,536,000	2,604,000	+68,000
Grants, subsidies, and contributions .	509,815,000	525,527,000	+15,712,000
Insurance Claims......................	162,000	167,000	+5,000
Interest	3,000	4,000	+1,000
Total	629,463,000	648,255,000	+18,792,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel compensation:			
Full-time permanent (11.1)	$22,217,000	$22,997,000	+$780,000
Other than full-time permanent (11.3)	7,828,000	8,117,000	+289,000
Other personnel compensation (11.5)	1,396,000	1,476,000	+80,000
Special personal services payments (11.8)	3,682,000	3,769,000	+87,000
Total personnel compensation	35,123,000	36,359,000	+1,236,000
Civilian personnel benefits (12.1)	7,267,000	7,610,000	+343,000
Benefits to former personnel (13.0)	200,000	50,000	-150,000
Travel (21.1)	995,000	1,039,000	+44,000
Transportation of things (22.0)	274,000	283,000	+9,000
Rental payments to other than GSA (23.2)	6,000	6,000	---
Communications, utilities, and miscellaneous charges (23.3)	1,679,000	1,673,000	-6,000
Printing and reproduction (24.0)	432,000	439,000	+7,000
Consulting service (25.1)	340,000	340,000	---
Other services (25.2)	10,163,000	9,876,000	-287,000
Purchases from Govt. accounts (25.3)	32,748,000	34,383,000	+1,635,000
Operation of GOCOs (25.4)	0	0	---
Supplies and materials (26.0)	5,418,000	5,535,000	+117,000
Total	94,645,000	97,593,000	+2,948,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
1995 House Report	
Parkinson's disease	
1. The House in its report 103-553, page 52 stated, "While recent scientific breakthroughs promise new avenues to understanding and treating Parkinson's disease, more research involving different Institutes and Centers is needed. The Committee therefore encourages NIH to convene a consensus conference in the near future to develop a coordinated research agenda among the Institutes which are studying Parkinson's."	1. In response to Senate report language for FY 1994, NIH submitted a report on NIH activities in Parkinson's disease. The 1994 report presented a comprehensive and well integrated research program for Parkinson's disease at the NIH, and included programs, research accomplishments, initiatives, and an assessment of research opportunities from eight NIH institutes and centers. NINDS and NIH institutes concerned with Parkinson's disease will also hold a conference in 1995 to further explore opportunities and issues in Parkinson's disease research and define an agenda for future work.
Lou Gehrig's disease	
2. The House in its report 103-553, page 52 stated, "The Committee encourages NINDS to consider establishing an intramural ALS research program as well as to continue funding extramural ALS research."	2. The extramural program in ALS is very active and productive, as evidenced by recent advances such as the development of an ALS mouse model and study of the SOD gene linked to a familial form of ALS. Decisions regarding the development of any new intramural programs await the appointment of a new scientific director and an evaluation of the overall intramural research program.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
Dystonia	
3. The House in its report 103-553, page 53 stated, "The Committee encourages NINDS to work closely with other organizations interested in dystonia research to collaborate on joint research programs encouraging investigators to study dystonia."	3. NINDS has taken several steps to encourage new efforts in dystonia research. In 1993, a workshop was held to focus on the current state of basic and clinical understanding of the dystonias with the intent of identifying promising new avenues of research. The workshop brought together investigators from across the country with interest in different aspects of dystonia research. A summary of the workshop, prepared by NINDS staff, was published in 1994 in a major science journal.
1995 Senate Report	
Dystonia	
1. The Senate in its report 103-318, page 82 stated, "The Committee encourages NINDS to work closely with other organizations having an interest in dystonia research to collaborate on joint research programs encouraging investigators to study dystonia."	1. NINDS has taken several steps to encourage new efforts in dystonia research. In 1993, a workshop was held to focus on the current state of basic and clinical understanding of the dystonias with the intent of identifying promising new avenues of research. The workshop brought together investigators from across the country with interest in different aspects of dystonia research. A summary of the workshop, prepared by NINDS staff, was published in 1994 in a major science journal.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
Stroke	
2. The Senate in its report 103-318, page 82 stated, "The Committee encourages the NINDS to expand its stroke education program and to continue and initiate innovative approaches to the diagnosis, treatment, rehabilitation, and prevention of stroke as identified by the National Advisory Neurological Disorders Stroke Council in "Progress and Promise 1992: Status Report for the Decade of the Brain."	2. NINDS will continue efforts to encourage new research studies in stroke. Results from NINDS-supported clinical trials continue to provide answers to long-standing questions of critical importance to stroke patients. In addition, progress is being made in basic laboratory research in which investigators are intensifying their efforts to understand the molecular mechanisms of stroke and develop pharmacologic interventions for the future. In 1994, NINDS published two new brochures on stroke. A third brochure is in preparation. In addition, NINDS has prepared and distributed a book marker listing risk factors and warning signs for stroke. Plans are underway to also distribute the marker through the public library system.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
Parkinson's disease	
3. The Senate in its report 103-318, page 82 stated, " ...the Committee is troubled that the disproportionately low level of resources devoted to research in this field as well as the absence of a coordinated research program will stymie efforts to capitalize on those breakthroughs. The Committee, therefore, directs that the National Institutes of Health convene a consensus conference as soon as possible, but not later than next year's hearings to develop a comprehensive plan for a coordinated research agenda among the National Institute for Neurological Disorders and Stroke, the National Institute of Aging, the National Institute of Environmental Health Sciences, and others as appropriate. In the interim, the Committee directs the NIH to reassess and increase its commitment of resources to research on Parkinson's disease.	3. In response to Senate report language for FY 1994, NIH submitted a report on NIH activities in Parkinson's disease. The 1994 report presented a comprehensive and well integrated research program for Parkinson's disease at the NIH, and included programs, research accomplishments, initiatives, and an assessment of research opportunities from eight NIH institutes and centers. NINDS and NIH institutes concerned with Parkinson's disease will also hold a conference in 1995 to further explore opportunities and issues in Parkinson's disease research and define an agenda for future work.
Lou Gehrig's disease	
4. The Senate in its report 103-318, page 82 stated, "The Committee encourages the Institute to build upon this promising development by expanding support for extramural amyotrophic lateral sclerosis (ALS) research as well as consider establishing an intramural ALS research program."	4. The extramural program in ALS is very active and productive, as evidenced by recent advances such as the development of an ALS mouse model and study of the SOD gene linked to a familial form of ALS. Decisions regarding the development of any new intramural programs await the appointment of a new scientific director and an evaluation of the overall intramural research program.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
Batten disease	
5. The Senate in its report 103-318, page 83 stated, "The Committee believes that the Institute should actively solicit quality grant applications for Batten's disease research and that it continue to take the steps necessary to assure that a vigorous research program is sustained and expanded. The Committee directs the Institute to provide sufficient funds to implement this objective."	5. The current level of research in Batten disease reflects extensive efforts to build a quality research program. Most recently, in 1994, NINDS issued a program announcement to solicit applications in neurogenetic disorders of infancy and childhood, including Batten disease. The current NINDS portfolio captures the leading research opportunities in Batten disease and is providing new information about the disease.
Ataxia-Telangiectasia (A-T)	
6. The Senate in its report 103-318, page 83 stated, "The Committee encourages continued A-T research and urges the NIH to consider sponsoring a workshop that would explore the causes, health consequences, biomedical research, and treatment potential for this disease. The Committee expects the workshop to be a collaborative effort with NCI, NCHGR, and NIA. The Committee also encourages the establishment of an A-T tissue and cell bank for public and private biomedical research."	6. NINDS supports studies on A-T and encourages new research efforts. For example, NINDS issued a program announcement in 1994, "Neurogenetic Disorders of Childhood," which included A-T. At this time, efforts by NIH to sponsor a workshop would largely duplicate workshops already sponsored by outside organizations concerned with A-T.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurolcgical Disorders and Stroke

Authorizing Legislation

	PHS Act / Other Citation	U.S Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation..	Section 301	42 §241	Indefinite	$615,264,000	Indefinite	$633,657,000
National Institute of Neurological Disorders and Stroke.................	Sections 457-459	42 §285j	Such sums as necessary		Such sums as necessary	
National Research Service Awards......................	Section 487	42 §288	Such sums as necessary	14,199,000	Such sums as necessary	14,598,000
Total Budget Authority......				629,463,000		648,255,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1987	$399,351,000	$491,085,000	$487,218,000	$490,233,000
1988	423,193,000	554,039,000	550,172,000	534,692,000 1/
1989 2/	557,585,000	557,046,000	477,878,000	567,690,000
1990	493,502,000	495,225,000	498,988,000	495,625,000 3/
1990 Sequester	---	---	---	-5,216,000
1991 4/	512,212,000	545,225,000	555,488,000	541,743,000 5/
1991 Sequester	---	---	---	-7,000
1992	583,355,000	583,355,000	583,386,000	577,938,000 6/
1993	615,190,000	605,100,000	607,100,000	600,078,000 7/
1994	590,065,000	630,650,000	630,650,000	630,650,000
1995 8/	630,443,000	626,471,000	628,801,000	627,726,000 9/
1996 8/	648,255,000			

1/ Includes funds for a reduction of $174,000 for travel and transportation costs.

2/ The House allowance excludes $14,210,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs. It excluded $93,100,000 for Other Communication Disorders (NIDCD). The appropriation included the budget for the NRSA program and provided $96,100,000 for the establishment of the proposed new institute, NIDCD.

3/ Excludes an enacted administrative reduction of $1,471,000.

4/ The House allowance excluded $13,016,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs.

5/ Excludes enacted administrative reductions of $15,121,000.

6/ Excludes enacted administrative reductions of $4,391,000 and an enacted rescission of $1,049,000.

7/ Excludes enacted administrative reductions of $6,522,000.

8/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

9/ Excludes enacted reductions of $321,000 for procurement, $33,000 for SLUC, and $221,000 for the limitation on 1% Bonus Pay.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Activity

(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Biological Basis research........	---	$284,791	---	$291,731	---	$308,063	---	$323,747	---	$335,722	---	+$11,975
Clinical research.	---	181,652	---	190,224	---	203,203	---	205,924	---	209,661	---	+3,737
Total extramural		466,443		481,955		511,266		529,671		545,383		+15,712
Intramural research.	540	70,934	503	72,563	474	73,222	486	73,027	481	75,351	-5	+2,324
Research management and support.......	209	25,821	206	26,532	195	25,800	194	26,765	192	27,521	-2	+756
Total, obligations..	749	563,198	709	581,050	669	610,288	680	629,463	673	648,255	-7	+18,792
Unobligated balance, lapsing...........		8		22		66		---		---		---
Total budget authority.......	749	563,206	709	581,072	669	610,354	680	629,463	673	648,255	-7	+18,792

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Neurological Disorders and Stroke

1994 Actual		1995 Appropriation		1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
669	$610,354,000	680	$629,463,000	673	$648,255,000	-7	+$18,792,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute of Neurological Disorders and Stroke. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The National Institute of Neurological Disorders and Stroke (NINDS) is the lead Federal agency for the support and conduct of research and research training on the normal function of the brain, spinal cord, and peripheral nerves, and on neurological and neuromuscular disorders. Brain disorders include stroke, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, head and spinal cord injury, Alzheimer's disease and other dementias, neuro-AIDS, muscular dystrophy, Parkinson's disease, neurofibromatosis, and Huntington's disease. Many neurological and neuromuscular disorders are chronic disorders, characterized by progressive decline in cognitive, sensory, or motor function over a long period, resulting in disability, suffering and long-term care at tremendous cost to the patient, family, and society. Permanent neurological disability that restricts daily activity affects Americans at an estimated cost of $400 billion each year.

Over the past year, NINDS grantees reported many new findings important to physicians, patients, and those at risk for neurological or neuromuscular disorders. As one example, results announced from two clinical trials give important new information to prevent stroke. Another clinical trial shows that we can reduce the extent and severity of brain bleeding in very low birth weight infants, thereby giving these children--who are otherwise at risk for neurodevelopmental handicap, mental retardation, seizures and cerebral palsy--a better chance in life. Through these and other discoveries research is changing the way health care professionals diagnose and treat neurological disorders, thus giving hope to millions of Americans.

These are pioneering times in the field of neurological research, as exemplified by research undertaken to explore how the brain performs the processes of thinking, remembering, and doing. For example, new brain-imaging technology permits scientists to observe the parts of the brain that work together when learning a task, and how these patterns of activity are altered in disorders of thinking or learning.

Today, some of the greatest opportunities to understand the brain and to find new treatments for brain disorders start with the discovery and study of genes. Genes are much more than a blueprint--as they are commonly described. In development and throughout life, genes are constantly being "turned on" and "turned off" in response to specific signals in the cellular environment. Genes are thus dynamic participants in the everyday function of the nervous system, responsible for guiding the production of the complex mixture of cellular proteins necessary for nerve cells to grow, to make connections, and to send and receive signals. Research studies supported and conducted by NINDS in FY 1996 will include efforts to map normal and defective genes, to identify their products and their functions, and, in cases of disease, to replace missing or defective genes or gene products. Transgenic animals, in which specific genes can be either inserted or "knocked-out," are proving to be powerful tools for investigating brain function. As one example, NINDS-supported scientists found in 1993 that a gene responsible for many cases of the familial form of amyotrophic lateral sclerosis (ALS) encodes superoxide dismutase (SOD), an enzyme that removes free radicals--highly reactive molecules that may play a deleterious role in several neurological disorders. That discovery has now led to the production of a transgenic animal model for the disease. Other studies investigating the role of genes in fostering or impeding recovery after stroke exemplify the potential of neurogenetic research even in "non-genetic" disorders.

In FY 1996, NINDS grantees and scientists will continue their efforts as part of the NIH-wide initiative in brain and brain disorders. The President's appropriation request of $648,255,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Neurological Disorders and Stroke during the last five years has been as follows:

	Amount	FTE
FY 1991	$525,674,000	740
FY 1992	563,206,000	749
FY 1993	581,072,000	709
FY 1994	610,354,000	669
FY 1995	629,463,000	680

Purpose and Method of Operation

Biological Basis Research stimulates and supports research on the structure and function of neurological systems. Clinical Research seeks to clarify pathological conditions and to develop methods for diagnosis, treatment, and prevention of these conditions. Technology transfer and communication among investigators are fostered by support of research workshops, symposia, and conferences. Extramural research support is provided through research grants, research center awards, research career program awards, research and development contracts, Small Business Innovation Research awards, and individual and institutional National Research Service Awards. The Intramural Research program conducts fundamental studies on brain structure and function as well as clinical research studies aimed at improved methods for the prevention, diagnosis, and treatment of neurological disorders.

Overall Budget Policy

The FY 1996 budget request for the NINDS is $648,255,000, an increase of $18,792,000 over the comparable FY 1995 level.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a 4.0 percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The NINDS FY 1996 budget request for research project grants is $451,881,000, an increase of $17,069,000 over the FY 1995 comparable level. This represents an increase of 3.9 percent. The total number of research project grants in FY 1996 is 1,845, as compared to 1,810 in the FY 1995 comparable level.

In FY 1996, the Institute will support 43 centers for $36,611,000, a decrease of $1,616,000 and three centers below the FY 1995 level.

Other research grants in FY 1996 will total 229 awards for $22,437,000, a decrease of $140,000 and one grant below the comparable FY 1995 level. For National Research Service Awards, an estimated 521 research trainees will be supported in FY 1996, the same number as the FY 1995 level.

The research and development contract budget of $19,856,000, will support 62 contracts, a decrease of three contracts below the comparable FY 1995 level.

The FY 1996 budget request for intramural research is $75,351,000, an increase of $2,324,000 from the comparable FY 1995 level. The request for research management and support is $27,521,000, an increase of $756,000 over the comparable FY 1995 dollar level. The number of FTEs in FY 1996 will be 673 compared to 680 in FY 1995.

National Institute of Neurological Disorders and Stroke

Extramural Research

Authorizing Legislation - Sections 301 and 457-459 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$511,266,000	$529,671,000	$545,383,000	+$15,712,000

The Extramural program includes research on the fundamental structure and function of the brain and nervous system; the causes and mechanisms of dysfunction of the nervous system; and research training in the basic neurological sciences. Clinical research is directed towards the solution of problems directly relevant to patients, including improved methods of diagnosis and prevention; development of treatments including drugs and surgery; development of neural prosthetic devices; epidemiological research; and research training in the clinical neurological sciences.

Funding for this program during the last five years has been as follows:

	Amount
FY 1991	$433,392,000
FY 1992	466,443,000
FY 1993	481,955,000
FY 1994	511,266,000
FY 1995	529,671,000

Rationale for Budget Request

The FY 1996 request is $545,383,000 an increase of $15,712,000 above the comparable FY 1995 estimate of $529,671,000. With the FY 1996 extramural request these funds will provide support for the following activities: Biological Basis Research, $335,722,000, an increase of $11,975,000 or 3.7 percent over the FY 1995 estimate of $323,747,000; Clinical Research, $209,661,000, an increase of $3,737,000 or 1.8 percent over the FY 1995 estimate of $205,924,000. The following are examples of research activities that will be funded in the Extramural Research Program in FY 1996.

Stroke

Stroke remains the third leading cause of death in the United States. Expenses due to stroke are estimated at $25 billion annually.

Stroke affects every age and population group in the country. The immediate cause of a stroke is a disruption in the blood supply to the brain, due, for instance, to a clot or clogged arteries. Some of the factors that set the stage for strokes to occur are well known--smoking, certain heart conditions, age--but these do not fully explain the reasons for stroke or provide the information needed for prevention and treatment. Through NINDS-supported research in FY 1996 including clinical trials, epidemiology studies, laboratory investigations, and studies of patients affected by stroke, scientists will continue to seek to find ways to prevent stroke and foster recovery from it.

Early endarterectomy shown to prevent stroke: Many strokes arise when narrowing of the carotid arteries in the neck reduces blood supply to the brain. A major trial just completed shows that surgery benefits those patients who have blockage of greater than 60 percent, but who have not experienced any warning symptoms of stroke. The results of the trial suggest that without surgery approximately 10 percent of patients with severe carotid narrowing will have a stroke after five years. For those that have surgery, the results of the trial predict a reduction of the stroke rate to 5 percent over 5 years. A previous NINDS trial showed that surgery also benefited patients with severe blockage (70 to 99 percent) of the carotid arteries who had already experienced symptoms of stroke.

Safer treatment for atrial fibrillation to prevent stroke: In 1994, NINDS grantees reported the results of the second in a series of clinical trials testing agents for preventing strokes in patients with atrial fibrillation. Atrial fibrillation is a common type of irregular heartbeat that increases the risk of stroke five-fold and is believed to cause about 70,000 strokes a year. An earlier trial--halted because of beneficial findings--had already established that patients with atrial fibrillation can lower their risk of stroke 50 to 80 percent by taking either aspirin or warfarin. The question remained as to whether aspirin, which is less expensive and less toxic, is as effective as warfarin. Because it is expensive and its use requires constant monitoring, some patients with atrial fibrillation have avoided using warfarin. This most recent trial showed that for most people with atrial fibrillation under 75 years old, and for those over 75 with no additional stroke risk factors such as high blood pressure or heart disease, the common drug aspirin provided adequate protection with minimal complications. Thus, the results of this trial may encourage more patients--without risk factors like hypertension or history of heart disease--to take aspirin as a preventive measure to reduce their risk of stroke. In FY 1996, NINDS will continue support of clinical studies to determine methods to prevent stroke in specific patient populations.

Neuronal nitric oxide exacerbates ischemic brain injury: Nitric oxide (NO), a gaseous chemical messenger used by the brain, is essential for many important body processes, but is also potentially toxic. Several types of brain cells produce NO, using forms of biosynthetic enzyme that are encoded by different genes. By "knocking-out" each gene, scientists can determine the function of NO produced by different cells. Recently, to investigate the role of NO in brain injury, stroke researchers developed a novel transgenic mouse that lacks only the gene for the enzyme that produces NO in neurons. Experiments that reduce blood flow to the brains of these mice show that NO from neurons exacerbates cell injury (ischemic injury) whereas NO from another source--blood vessels--protects cells. These results give impetus to the search for selective inhibitors of NO production that might be used therapeutically. In FY 1996, further study of transgenic animals with such well defined single gene alterations will lead to additional new insights into the causes of ischemic neuronal injury and lead the way to novel therapeutic approaches for stroke.

Antisense inhibition of gene expression in stroke: One current model of brain injury caused by stroke postulates that the entry of calcium into neurons through a specific type of glutamate receptor (the NMDA receptor) leads to neuronal injury and death. This hypothesis has recently been given strong support by experiments using a novel strategy (antisense oligonucleotides) to block synthesis of the NMDA receptor. Animals whose brains were treated by this technique were more resistant to ischemic injury than were normal animals. This novel approach will facilitate investigation in FY 1996 of the role of other molecules in stroke, and provides a potentially innovative means of stroke therapy.

Central Nervous System Development

Neural tube defects: Development of the nervous system occurs through an ordered, highly coordinated progression of gene expression. In the last few years, much has been learned about the genes that determine patterning in the brains of simple organisms, such as fruit flies. Remarkably, genes originally identified in such simple species often have a counterpart in humans that serves a similar function. Studies are in progress to understand the role of one such group of genes (known as Pax genes) in the developing mammalian nervous system, where they are believed to regulate the formation of neural structures before birth. During embryo formation, one Pax gene, Pax-3, appears to be important for formation of the neural tube, the precursor of the brain and spinal cord. Although the exact role of Pax-3 in neurulation remains unclear, mutations in Pax-3 result in neural tube defects such as exencephaly (part of the brain is exposed) or spina bifida (incomplete closure of the spinal column). Defects in the Pax-3 gene appear to be the basis for the human disease, Waardenburg syndrome. Both patients with the disease and animals with a model of the disease (splotch mutant mice) have mutations in the Pax-3 gene. In FY 1996, additional studies on Pax-3 and the splotch mice will shed new light on this disease and on the mechanism of neural tube formation.

Rare Disorders of the Nervous System

Most individual neurological disorders are uncommon; in fact, more than 600 disorders afflict the human nervous system. Research on rare diseases is important not only because it leads to diagnosis and treatment of the disease, but also because it can provide insight into fundamental mechanisms relevant to other neurological disorders.

Mechanism of genetic defect common to several disorders: One of the most exciting recent advances in neurogenetics (and one that will be further explored in research efforts in FY 1996) is the discovery of a similar type of genetic defect found in several different neurological diseases. Genes are linear sequences of four different "building blocks," the bases A, T, G, C. What scientists have found in fragile X syndrome, myotonic dystrophy, spinobulbar muscular atrophy, Huntington's disease, and spinocerebellar ataxia type I (SCA1), is a deranged pattern in which three of the bases are repeated numerous times--a trinucleotide repeat. For instance, in 1993, the Huntington's Disease (HD) Collaborative Research Group, involving nine institutions, with major support from NINDS, reported that people with HD have a three base sequence (CAG) on chromosome 4 that is replicated 37-100 times, compared to 6-34 times in normal subjects. In the past year, scientists have reported that the length of the trinucleotide repeat correlates with the age of onset. For example, the longest repeats appear in juvenile onset HD. Attempts by a number of groups are now being made to understand why an increased number of repeats leads to neuronal degeneration, with resulting disease.

Progress in Batten disease: Batten disease and other forms of the neuronal ceroid lipofuscinoses (NCL) occur in an estimated 2 to 4 of every 100,000 live births in the United States, causing encephalopathy, loss of vision, and seizures. Researchers have identified the material that accumulates in the infantile form of NCL. The major portion of the accumulated protein consists of saposins A and D (also known as sphingolipid activator proteins or SAPs). This is interesting because it was previously shown that in the late infantile and juvenile forms of NCL, a different substance accumulates (subunit c of mitochondrial ATP synthase). Although this is the first time SAPs have been found stored in any type of NCL, they have been found in cells from patients with other disorders (such as Gaucher's disease and Tay-Sachs), as a consequence of an enzyme defect. In FY 1996, further studies will help to elucidate the mechanism of the defect in the infantile form of NCL, which may be helpful in understanding other forms of Batten disease.

Nerve cell growth and survival: Many neurological diseases (Alzheimer's, Parkinson's, ALS, Huntington's) arise because discrete populations of cells degenerate and die. It is thus important to understand the factors that sustain the survival and growth of neurons and their supporting glial cells. Research in this area will continue to be supported in FY 1996. For example, recently, a growth factor (GDNF or glial-derived neurotrophic factor) known to be required for the survival of dopamine-containing neurons has been shown to be the most powerful factor yet found in supporting the survival of the spinal motoneurons that innervate muscles. This finding now prompts further study of the possible use of GDNF as a treatment for motoneuron disease. In other studies, two growth factors (the neurotrophin nerve growth factor or NGF and the neurokine ciliary neurotrophic factor or CNTF) have been found to use different signal transduction systems to induce the expression of a single gene in neuronal cells. Understanding these signaling pathways may allow the design of specific therapeutic agents that will selectively alter the different intracellular pathways. Another approach to understanding cell survival is to study the "programmed" death (known as apoptosis) of neurons and other cells that occurs during development. Recently scientists have found that a protein that protects one type of white blood cell from apoptosis also protects neurons from cell death following injury.

At points of contact (synapses), neurons signal to each other by rapidly secreting chemical messengers called neurotransmitters in response to electrical impulses. Scientists have recently begun to isolate the molecules responsible for this rapid secretion. One of them, synaptotagmin, may be the molecule that triggers secretion by binding calcium. Mice in which the synaptotagmin gene has been "knocked-out" are unable to rapidly secrete neurotransmitter in response to an electrical signal, whereas other forms of secretion remain intact.

The efficiency of signalling at synapses can be altered by prior experience; such experience-dependent alterations are thought to underlie memory and learning. Recent research has used "knock-out" mice to show that protein kinases play an important role in the stable enhancement of synaptic transmission called "long-term potentiation." Scientists have also recently found that synaptic transmission can not only be augmented, but also reduced ("long-term depression") by prior experience. The molecular mechanisms of these processes and their role in learning remain active areas of investigation, and will continue to be explored in FY 1996.

A transcription factor required for long-term memory: Recent work in fruit-flies by NINDS-sponsored investigators has shown that separate, parallel pathways are involved in long and short-term memory and that a factor (CREB) responsible for turning on genes in response to hormones is required for long-term, but not short-term memory. Flies in which the action of this protein was blocked, were able to learn and remember a task one day after learning, but, unlike normal flies, were unable to retain the memory when tested seven days later. Experiments by others have extended these results to mammals, showing that mice in which this gene is "knocked-out" are profoundly deficient in long-term memory and show defective long-term potentiation. Through continued research efforts in FY 1996, these results should help us better understand the deficiencies in memory exhibited in neurological disease and pave the way for thinking about rational therapies for memory loss.

Neurodegenerative disorders

In Parkinson's disease dopamine-producing cells in the substantia nigra are lost, whereas Huntington's disease is characterized by degeneration of the striatum, a part of the brain that helps control motor function. Through research to be supported in FY 1996, leading to improved understanding of the processes underlying brain degeneration in these and other disorders, we may be able to devise strategies to delay progression of a particular disease; ameliorate the disease to preserve a level of function compatible with independent living; and, perhaps one day, to prevent disease altogether.

For example, in one group of neurodegenerative diseases (the spongiform encephalopathies, including Creutzfeld-Jakob disease, mad cow disease, and scrapie), disease transmission is thought to occur through a biologically novel mechanism in which the infectious agent, a modified form of the prion protein, converts the normal host prion protein to the infectious form. Recent experiments offer important support for this hypothesis by showing that when animals lacking the prion protein are injected with the infectious agent they do not develop the disease and show no increase in infectious activity. Thus the normal protein is essential both for development of the disease and for its propagation.

Parkinson's Disease: Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder of movement which severely incapacitates large numbers of adult Americans. Lesions in the brains of patients with Parkinson's disease have long been known to reduce tremor, although the mechanism of action is not always clear and early procedures carried a considerable risk of side effects. One such surgical procedure, pallidotomy, has been refined and is now being evaluated in a clinical trial funded during the past year. Other research efforts that will continue to be supported and conducted by NINDS in FY 1996 in Parkinson's disease include work on causes, such as environmental and endogenous toxins; genetic predisposition; altered motor circuitry and neurochemistry; and the search for other new therapeutic interventions. NINDS and NIH institutes concerned with Parkinson's disease will hold a conference in 1995 to explore opportunities and issues in Parkinson's disease research and to define an agenda for future work.

Amyotrophic Lateral Sclerosis: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a degenerative disease of motor function that affects an estimated 13,000 to 20,000 Americans each year, causing progressive paralysis and inevitable early death. Building upon the recent discovery that a significant number of familial amyotrophic lateral sclerosis (ALS) patients have mutations in an enzyme (Cu, Zn superoxide dismutase or SOD), NINDS grantees have produced transgenic mice that express wild type or mutant forms of SOD. These mice develop weakness and neuronal degeneration similar to that seen in ALS patients. Through research to be supported in FY 1996, this important new model should yield insights into the pathogenesis of this disease and provide an animal system for testing therapies for the disease.

Epilepsy

Twenty million Americans will have at least one seizure during their lives, and 2.5 million will have the disorder of spontaneously recurrent seizures known as epilepsy. Epilepsy research spans studies of basic mechanisms, etiologies, prevention, diagnosis, and treatment. Specific efforts that will continue to be supported in FY 1996 include seizure mechanisms in the developing brain, epidemiology of epilepsy, clinical studies of therapeutic treatments to control epilepsy, surgical therapies of epilepsy, brain imaging studies, and genetic factors in epilepsy.

The search to identify and characterize the underlying disease mechanisms of various seizure disorders has been the focus of many investigations. A recent major finding has been the discovery that one disorder, Rasmussen's encephalitis, may be due to an autoimmune response, as indicated by antibodies to one type of glutamate receptor. Over the past several years, epilepsy genes have been localized to particular chromosomes in juvenile myoclonic and related epilepsies, benign familial neonatal convulsions, and Baltic type progressive myoclonic epilepsy. The search continues to isolate and clone the specific genes.

The molecular basis for the development of epilepsy is being investigated using seizures produced by a process called kindling. Scientists have now demonstrated that kindling induces the expression of a previously unknown form of the NMDA receptor for glutamate. The behavior of this novel receptor may help explain the vulnerability of specific structures of the brain (mesial temporal lobe structures) to the generation of epilepsy in response to kindling. Further study in FY 1996 may lead, in turn, to better understanding of the vulnerability of these same brain structures to prolonged febrile seizures, a common clinical problem.

Head and Spinal Cord Injury

Over 2 million head injuries occur each year. Approximately 100,000 victims die and 500,000 require hospitalization. Traumatic brain injury (TBI) is considered the principal cause of permanent brain damage in young adults and results in 5,000 new cases of epilepsy annually. The economic costs alone approach $25 billion per year. Traumatic spinal cord injury claims approximately 10,000 new victims each year.

Early neurofilament derangement in brain trauma: Dendrites and axons are extensions from nerve cells which serve as the primary points for nerve cells to receive (dendrites) and send (axon) electrochemical signals. Investigators have long recognized that diffuse axonal injury is a major pathological feature of traumatic brain injury. However, until recently, we had a limited understanding of the biochemical and structural mechanisms underlying this type of damage. Investigators now have identified early structural derangements in the cytoskeletal proteins, NF-H and NF-L in both axons and dendrites that are pivotal in the development of subsequent reactive changes. These findings in humans corroborate earlier studies in animal models. Most important, the studies suggest that neurofilament derangements can serve as markers for the injured neurons, and suggest potential therapies to counteract their destruction. Many NINDS funded laboratories are currently investigating novel approaches for preventing early loss of these important structural proteins. Future studies on diffuse axonal injury should provide more focused investigations on the early subcellular events responsible for these cytoskeletal abnormalities. These studies provide important therapeutic potential for the treatment of brain injured patients, and will continue in FY 1996.

Familiar protein provides new clue to nerve regeneration: One reason for the severity of neurological disease is that neurons in the brain and spinal cord, unlike those in the periphery, fail to regenerate after damage to their axons. In recent years, scientists have found that this failure may be partially explained by factors in the brain and spinal cord that inhibit axonal growth. One such factor that has recently been identified is myelin-associated glycoprotein (MAG), a well-known component of myelin, the membranous sheath around axons that increases their ability to conduct electrical signals. This discovery comes as a surprise, since MAG is thought to stimulate growth in peripheral nerves, although its role in the CNS has not been elucidated. The exciting findings with MAG offer new clues toward understanding the old problem of why injured neurons fail to regenerate in the CNS. In FY 1996, studies with transgenic mice that lack the MAG gene should provide more direct evidence.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the nervous system presumed to be of autoimmune origin. MS appears to be influenced by a combination of genetic, viral, immune, and perhaps other unknown factors. In MS, the myelin which surrounds nerve fibers in the brain and spinal cord is destroyed, fails to re-form, and develops into scar tissue resulting in neurological dysfunction. There are an estimated 250,000 to 300,000 MS patients in the U.S., representing an economic burden believed to be in excess of $2.5 billion annually. Studies of immune characteristics of MS patients and abnormalities found in animal models will continue. In FY 1996, the Institute plans to continue to support fruitful avenues of research such as mechanisms of pathogenesis and plaque formation, role of heat shock proteins, remyelination, genetic susceptibility, clinical studies of cytokines, use of peptides in regulation/blocking of immune responses, development of new monoclonal antibodies, and studies of adhesion molecule function in cell traffic across the blood brain barrier.

Restitution of Function

Several avenues are being pursued by NINDS grantees to restore nervous system function. One such strategy is the development of neural prostheses--devices that interface with the nervous system to restore sensation or movement. Already this program has yielded: a hand-grip prosthesis that enables paralyzed people to pick up objects or to grasp a cup and drink without assistance; tiny electrodes, measuring about one-third the width of a human hair, that can be implanted inside the body and used to stimulate muscle or nerve cells; new understanding of the nervous system and its pathways that will help scientists place future prostheses in the most effective location; and artificial sensors that may help paralyzed patients to better control movement. NINDS anticipates funding additional investigator-initiated applied, basic, and clinical research on restoration of nervous system function in FY 1996.

Research Training and Career Development

The Institute will continue to encourage and support research training on the fundamental structure and function of the brain and nervous system and the causes and pathophysiology of dysfunction in the nervous system. In the basic neurological sciences, areas of emphasis include molecular biology, cognitive science, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neurosensory physiology and biophysics, and neurovirology. The Institute also provides clinical research training through individual National Research Service Awards and institutional National Research Service Awards. These programs train personnel for academic careers in research aimed at developing improved diagnosis, treatment and, where possible, prevention of human nervous disorders. Major clinical areas of research training include: cerebrovascular disorders (including stroke), medical neurology, neuromuscular disorders, neurosurgery, neuroepidemiology and neuropathology.

Career development is supported through the Research Career Program which includes Research Career Development Awards (RCDA), and Clinical Investigator Development Awards (CIDA). The NINDS has established a program for re-entry into the neurological sciences (RENS) to help scientists who have experienced an interruption in their research careers to re-enter active careers in neurological sciences research. The Neurological Sciences Academic Development Award (NSADA), an institutional award, has been established on a pilot basis in pediatric neurology for physicians in residency training to have exposure to research career opportunities. These programs will continue in FY 1996.

National Institute of Neurological Disorders and Stroke

Extramural Research

	1995 Appropriation	1996 Estimate	Change
Impact Data			
Neurological disorders of early life	$81,972,000	$84,335,000	+$2,363,000
Neurological disorders of adult life	42,568,000	43,758,000	+1,190,000
Stroke	64,966,000	67,066,000	+2,100,000
Epilepsy	46,549,000	47,833,000	+1,284,000
Demyelinating disorders	33,510,000	34,434,000	+924,000
Neuromuscular disorders	25,065,000	25,817,000	+752,000
Infectious diseases of the central nervous system	12,213,000	12,551,000	+338,000
Trauma and injury	68,712,000	70,909,000	+2,197,000
Tumors	11,574,000	11,849,000	+275,000
Disorders due to neurotoxicants	2,653,000	2,749,000	+96,000
Neuroendocrine and autonomic nervous system	21,067,000	21,622,000	+555,000
Learning, language and behavior	16,489,000	16,930,000	+441,000
Nervous system function	74,027,000	76,265,000	+2,238,000
Metabolism and nutrition	2,536,000	2,620,000	+84,000
Neurosensory disorders	13,318,000	13,762,000	+444,000
Multicategorical research	6,326,000	6,543,000	+217,000
Neural Prostheses	6,126,000	6,340,000	+214,000
Total	529,671,000	545,383,000	+15,712,000

National Institute of Neurological Disorders and Stroke

Intramural Research

Authorizing Legislation: Sections 301 and 457-459 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
474	$73,272,000	486	$73,027,000	481	$75,351,000	-5	+$2,324,000

The research efforts of this program range from fundamental studies on nerve cell development, structure, and function to clinical research aimed at improved methods for the diagnosis, treatment, and prevention of neurological disorders and restitution of function. Intramural clinical studies are primarily in chronic, infectious, or degenerative neurological disorders and typically involve study of a small group of patients over a long period of time. The clinical expertise and available facilities are especially beneficial for the study of the many rare neurological disorders. Intramural studies often involve the development of leading edge technologies and treatments which may include extensive collaborations with extramural investigators and provide a research base for further studies. Research using brain imaging techniques examines the metabolic and anatomic changes in brains of patients with disorders of the nervous system.

Funding for Intramural Research during the last five years has been as follows:

	Amount	FTE
FY 1991	$67,875,000	537
FY 1992	70,942,000	540
FY 1993	72,563,000	503
FY 1994	73,272,000	474
FY 1995	73,027,000	486

Rationale for Budget Request

The FY 1996 budget request for intramural research is $75,351,000 an increase of $2,324,000 from the comparable FY 1995 level of $73,027,000. The following are examples of research activities to be funded in the Intramural Research Program.

Genes that regulate the production of myelin in the brain: Oligodendrocytes are the cells in the brain that make the wrapping, called the myelin sheath, that envelopes neurons and allows them to operate efficiently. The process involves the production of vast amounts of proteins and lipids in the correct proportions needed for a myelin sheath. When one of these myelin proteins is missing, defective, or present in the wrong amount, the myelin sheath cannot be properly formed or maintained.

Intramural scientists have now discovered one way that an oligodendrocyte matches the production of myelin lipids with that of myelin proteins. To accomplish this task, oligodendrocytes employ members of the nuclear hormone receptor family, which are regulatory molecules that form partnerships with one another prior to binding target genes. Intramural scientists have found that the thyroid hormone receptor regulates the gene encoding the major myelin protein only when it chooses a particular receptor, the PPAR receptor, as its partner. As PPAR is responsible for activating genes involved in myelin lipid metabolism, the partnership between the two receptors thus links protein and lipid synthesis in oligodendrocytes. Research conducted in FY 1996 will further increase understanding of how myelin lipid and protein production are regulated.

Brain Tumor: In FY 1996, NINDS scientists will continue to investigate new strategies to treat brain tumors. NINDS intramural scientists are investigating a novel approach for the treatment of brain tumors by utilizing a new class of potent, targeted anti-cancer compounds that are made in the laboratory by coupling proteins to toxins. Laboratory experiments have demonstrated that these targeted protein toxins have significant antitumor activity against a variety of tumor types. A new method of drug delivery to deliver these agents to brain tumors and in vivo imaging methods to visualize their distribution in patients are being developed.

Stroke: In FY 1996, studies conducted in the intramural program will continue to seek to improve understanding of the factors that increase stroke likelihood. These studies focus on the procoagulant and proinflammatory effects of cytokines (intercellular signalling molecules) on the cells lining blood vessels and the role of these molecules in the genesis of stroke. This work should ultimately help reduce the odds of having a stroke.

Multiple Sclerosis: In FY 1996, the intramural program will continue studies using magnetic resonance imaging (MRI) to examine the natural history of multiple sclerosis during the early mild, relapsing-remitting phases of the disease. These studies have found that many patients have substantial evidence of disease even during its early, apparently inactive phase. The effect of interferon beta 1b, a recently approved therapy in MS, has now been studied in a group of 14 patients with early mild, relapsing-remitting MS to test its ability to reduce alterations in the blood-brain barrier as measured by gadolinium-enhanced MRI. In those studied, all have a dramatic reduction in lesions, with complete cessation of disease activity, as measured by MRI, for many. These findings suggest an important site of action for beta-interferon, and point to new avenues of research to be pursued.

Magnesium exposure in utero and reduction of cerebral palsy in very low birthweight infants: An NINDS scientist, in collaboration with the California Birth Defects Monitoring Program (BDMP), has found that administration of magnesium sulfate to mothers before and during preterm delivery is associated with striking reduction in the frequency of cerebral palsy in very low birthweight infants born of those deliveries. The magnesium sulfate was provided to the mothers as a therapy for preterm labor or to prevent convulsions associated with a complication of pregnancy, known as preeclampsia. NINDS is cooperating with the California BDMP, the Centers for Disease Control and Prevention, and other institutes in planning further efforts to validate and expand on this observation.

National Institute of Neurological Disorders and Stroke

Research Management and Support

Authorizing Legislation: Sections 301 and 457-459 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
195	$25,816,000	194	$26,765,000	192	$27,521,000	-2	+$756,000

Research Management and Support includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of research grant, research contract, and research training programs. This activity also supports the immediate Office of the Director, and the staff that assists the Director in management and direction of the Institute's programs. These units include the administration and financial management activities of the Institute as well as program analysis functions and scientific and health reporting.

Funding for the Research Management and Support during the last five years has been as follows:

	Amount	FTE
FY 1991	$24,395,000	203
FY 1992	25,821,000	209
FY 1993	26,554,000	206
FY 1994	25,816,000	195
FY 1995	26,765,000	194

Rationale for Budget Request

The FY 1996 budget request for research management and support is $27,521,000, an increase of $756,000 over the comparable FY 1995 level of $26,765,000.

84

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	68	68	69
Division of Fundamental Neurosciences	9	9	8
Division of Stroke and Trauma	9	9	8
Division of Extramural Activities	65	64	62
Division of Convulsive, Developmental, and Neuromuscular Disorders	37	37	38
Division of Demyelinating, Atrophic, and Dementing Disorders	7	7	7
Division of Intramural Research	474	486	481
Total, NINDS	669	680	673

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1991	9.6
1992	9.7
1993	9.9
1994	9.9
1995	9.9
1996	9.9

National Institute of Neurological Disorders and Stroke
Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Appropriation	1996 Estimate
ES-6	1	1	1
ES-5	1	1	1
ES-4	12	9	8
ES-3	1	1	1
ES-2	1	1	2
ES-1	2	2	1
Subtotal	18	15	14
Total - ES Salary	$1,900,100	$1,996,400	$2,077,000
GS/GM-15	30	30	29
GS/GM-14	43	43	42
GS/GM-13	45	45	44
GS-12	47	47	47
GS-11	67	67	67
GS-10	5	5	5
GS-9	42	42	42
GS-8	34	34	34
GS-7	66	66	66
GS-6	37	37	37
GS-5	23	23	23
GS-4	22	22	22
GS-3	13	13	13
GS-2	4	4	4
Subtotal	478	478	475
Grades established by Act of July 1, 1944 (42 U.S.C. 207)			
Assistant Surgeon General			
Director Grade	18	18	18
Senior Grade	8	8	8
Full Grade	15	15	15
Senior Assistant Grade	4	4	4
Subtotal	45	45	45
Ungraded	125	128	128
Total permanent positions	503	503	501
Total positions, end of year	680	673	666
Total full-time equivalent (FTE) employment, end of year	669	680	673
Average ES level	3.7	3.7	3.7
Average ES salary	$105,561	$108,960	$111,357
Average GS/GM grade	9.9	9.9	9.9
Average GS/GM salary	$43,555	$45,314	$47,145

THURSDAY, MARCH 30, 1995.

NATIONAL CANCER INSTITUTE

WITNESSES

EDWARD J. SONDIK, ACTING DIRECTOR
DR. BRUCE CHABNER, DIRECTOR, DIVISION OF CANCER TREATMENT
PHILIP D. AMORUSO, ASSOCIATE DIRECTOR FOR ADMINISTRATIVE MANAGEMENT
JOHN P. HARTINGER, FINANCIAL MANAGER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANAYSIS, DHHS

Mr. PORTER. The subcommittee will come to order.

We are returning today to the Department of Health and Human Services because of a need to postpone hearings earlier due to full Committee meetings. We are pleased to welcome Dr. Edward J. Sondik, Acting Director of the National Cancer Institute this morning.

Dr. Sondik, why don't you introduce the people at the table with you and then proceed in any way you wish?

INTRODUCTION OF WITNESSES

Dr. SONDIK. Thank you very much.

Let me start on my right. Bill Beldon is representing the Department; Dr. Varmus, whom you have met before; Bruce Chabner, Director of the Division of Cancer Treatment; John Hartinger, our Budget Officer; and Phil Amoruso is the Executive Officer.

OPENING STATEMENT

Mr. Chairman, thank you for the opportunity to testify on behalf of the National Cancer Institute. We face a continuing challenge to generate the knowledge to reduce deaths and suffering from cancer.

The need is clear. Cancer incidence and mortality rates, on the whole, continue to rise. This year 1.2 million Americans will be diagnosed with cancer and about 547,000 will die of this disease. Only four cancers account for over half of all cancer deaths—breast, prostate, lung, and colorectal cancers. Looking at these cancers, we see a mixed picture with lung cancer deaths declining for men but not women and fewer deaths from colorectal cancer but more deaths from prostate cancer.

On a very positive note, I am pleased to report that we recently found that deaths from breast cancer declined by over 5 percent from 1989 to 1992, due we believe to advances in therapy and screening. However, this decline was only seen among whites. The African American population experienced a 2 percent increase. In fact, African Americans have higher incidence and death rates for cancer overall. We need to find the causes of these differentials and ensure that all Americans benefit from NCI's supported research.

To meet the challenge of cancer, the NCI is structured on investigator-initiated research that leads to prevention and treatment clinical trials, all supported by a nationwide network of cancer centers. We support a full spectrum of research from basic to applied, and from prevention to treatment to surveillance to control.

Basic research is fundamental to understanding cancer and the gene-based control mechanisms that, when awry, lead to the uncontrolled cell growth that characterizes cancer. Basic research, coupled with clinical research, has led not only to new drugs such as a semi-synthetic Taxol now used against some breast and ovarian cancers, but also has led to genetically engineered agents to treat cancer or to prevent its spread throughout the body. In a novel treatment approach born of basic research, NCI-supported scientists are borrowing from cardiovascular research to find ways to interrupt the development of the blood supply to tumors and thereby limit the ability of the cancer cells to multiply.

Other new experimental treatment approaches include vaccines, tumor-specific customized therapies, immunostimulants, and specially constructed antibodies which can carry a therapy right to a cancer cell. Research on gene therapy, to replace or repair damaged genes or gene products, has given us a new approach to treatment. Developed in the NCI intramural program, gene therapy well illustrates translational research—research linking the laboratory to the clinic. Today, across the United States, there are over 70 experimental gene therapy protocols for cancers such as melanoma, lung and kidney cancers, ovarian and breast cancers, lymphomas, leukemias and brain cancers, as well as immune disorders, cystic fibrosis, and cardiovascular disease.

To foster the translation of basic discoveries into clinical prevention and treatment research, NCI introduced the SPORES program, Specialized Programs of Research Excellence, in which multidisciplinary teams work to develop new technologies for preventing and treating breast, prostate, lung, GI, and other cancers.

Over the past several years, NCI's collaboration with the National Center for Human Genome Research has brought an explosion of information about genes associated with cancer. This year we had the long-awaited news that BRCA–1 was located on chromosome 17. This gene is linked to a family susceptibility not only to breast cancer but also ovarian, colon, and possibly prostate cancer. BRCA–2, a second familial breast cancer gene, has also been located. Each genetic discovery may lead to new diagnostic tests, preventive approaches, and therapies. Several new urine or blood-based gene tests are already a reality.

In addition to the gene-based tests to identify risk, research on cancer detection and screening includes technologies such as magnetic resonance imaging, computer-assisted radiology, ultrasound, and positron emission tomography, all aimed at better ways to image tumors. And in our PLCO trial, screening for prostate, lung, colorectal, and ovarian cancers, we are evaluating blood-based PSA (prostate specific antigen) tests for prostate cancer and the CA–125 test for ovarian cancer.

Epidemiology studies are especially important in identifying causes of cancer. The Long Island Breast Cancer Study focusing on high rates of breast cancer and the Agricultural Health Study examining cancer among farm workers and their families are two examples of research investigating the world of the environment and cancer. The Long Island study is especially notable for its development of new methodologies and its forging of close collaborations among Federal and State agencies, as well as community-based research institutions.

NCI-supported research has revealed a great deal about the development of cancer and the interaction of environmental factors and occupational hazards, including radiation, chemicals, pesticides, and viruses. Recent NCI-supported studies have shown that helicobacter pylori, a common infection, is associated not only with ulcers but with stomach cancer and a form of lymphoma.

The growing evidence that many cancers may be preventable has opened a wide new area of cancer research. NCI's program includes nutritional, chemopreventive, behavioral, and other approaches to inhibit, delay, or reverse cancer development. Several new prevention clinical trials are underway, including one for breast cancer using tamoxifen and another for prostate cancer using finasteride or Proscar. Progress toward prevention of these highly prevalent cancers would save thousands of lives every year.

Perhaps the two strongest factors related to cancer prevention are tobacco and diet. We know from both laboratory and epidemiology studies that the relationship of diet to cancer is very strong. In 1982, NCI began a cancer prevention and control program to further our knowledge in this area. We have learned, for example, that the retinoids, a class of compounds including Vitamin A, have been shown to suppress tumor growth in many types of cancer, including the skin, lung, and mouth. We have found that some micronutrients detoxify, others inhibit cell signaling, some stimulate the immune system. It is vitally important to continue to test these agents in clinical trials.

We must never forget, however, the patient who struggles with cancer today. To help patients and their families and to provide physicians with the latest information, NCI uses fax-based and on line Internet-based systems as well as other computer databases to diffuse the best information about cancer and cancer treatment. Certainly the most ubiquitous source of information is the nationwide toll-free 1–800–4–CANCER telephone number that reaches NCI's Cancer Information Service and its trained counselors.

Women's health, specifically cancers that threaten survival, receives a high priority at NCI. The institute participates in the NIH Women's Health Initiative which focuses on the prevention of three major killers—breast cancer, heart disease, and osteoporosis. We lead a working group to coordinate breast cancer research throughout NIH and we are partners with the Department's Office of Women's Health to implement the Secretary's Breast Cancer Action Plan.

Mr. Chairman, virtually every American family feels pain and suffering from cancer. Four in ten of us will develop cancer and one in five of us will die of cancer. So while our knowledge about cancer has increased, a great deal remains to be learned. The challenge of cancer is formidable. Even the rapid uncovering of genetic information raises other issues. We cannot simply mark a person as having a cancer gene and then walk away. We must consider counselling and privacy issues and, of course, the question of prevention as well as appropriate treatment.

Thank you for your attention. The fiscal year 1996 budget request for the National Cancer Institute totals $1,994,007,000 for cancer research, an increase of $76,103,000. Funds for AIDS research at NCI are requested by the NIH Office of AIDS Research.

[The prepared statement and biography of Dr. Edward Sondik follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Acting Director
National Cancer Institute

Mr. Chairman, thank you for the opportunity to testify on behalf of the National Cancer Institute.

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On a very positive note, I am pleased to report we recently found that deaths from breast cancer declined by over 5 percent from 1989 to 1992, due, we believe, to advances in therapy and screening. However, this decline was seen only among whites. The African American population experienced a 2 percent increase. In fact, African-Americans have higher incidence and death rates from cancer overall. We need to find the causes of these differentials and ensure that all Americans benefit from NCI-supported research.

To meet the challenge of cancer, the NCI is structured on investigator-initiated research that leads to prevention and treatment clinical trials, all supported by a nationwide network of cancer centers. NCI supports a full spectrum of research from basic to applied, and from prevention to treatment to surveillance to control.

Basic research is fundamental to understanding cancer and the gene-based control mechanisms that, when awry, lead to cancer's uncontrolled cell growth. Basic research, coupled with clinical research, has led not only to new drugs such as a semi-synthetic Taxol, now used against some breast and ovarian cancers, but also has led to genetically-engineered agents to treat cancer or to prevent its spread throughout the body.

In a novel treatment approach born of basic research, NCI-supported scientists are borrowing from cardiovascular research to find ways to interrupt the development of the blood supply to tumors and limit the ability of the cancer cells to multiply.

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I thank you for your attention. The 1996 budget request for the National Cancer Institute totals $1,994,007,000 for cancer research, an increase of $76,103,000.

EDWARD J. SONDIK, Ph.D.
Biographical Sketch

Dr. Sondik has been appointed Acting Director, National Cancer Institute (NCI) effective March 1, 1995, by Dr. Harold Varmus, Director of the National Institutes of Health (NIH). He has served as the Acting Deputy Director, NCI, since February 1994. The NCI is the preeminent Federal agency for cancer research and is one of the National Institutes of Health. The NCI Director leads the National Cancer Program and the cancer-related activities at NIH. The Director, NCI, is responsible for providing guidance and staff direction to the Institute's programs in such areas as program coordination, program planning, clinical care and administrative management.

During his tenure as Acting Deputy Director of NCI, Dr. Sondik assisted the Director in policy development and analysis as well as the overall management of the Institute. Dr. Sondik played an important role in reviewing NCI clinical trials with an emphasis on quality assurance. He has coordinated activities related to the cancer objectives of the Department of Health and Human Services *Healthy People 2000* Initiative. Actively concerned with the issues surrounding mammography, Dr. Sondik recently provided the leadership and oversight of deliberations regarding breast cancer early detection in women under 50 years of age. Dr. Sondik was also responsible for coordinating a planning conference related to breast imaging technologies in response to the Secretary's National Action Plan on Breast Cancer. He is the NCI contact for that Plan.

Dr. Sondik has been at the NIH since 1976. From October 1982 through September 1989, he served as the Associate Director of the Division of Cancer Prevention and Control (DCPC) and led the Institute's Surveillance, Epidemiology, and End Results Program (SEER). Dr. Sondik left that position to become Deputy Director of the DCPC.

Dr. Sondik's activities in this position have included Co-Editorship of the NCI Monograph on Cancer Control Objectives, development of a series of reports on cancer surveillance, and expansion of cancer surveillance activities to include aspects of health services and public and professional knowledge, attitude, and practice. Dr. Sondik also chairs the Special Action Committee, formed by the NCI Director to review the Institutes's activities and program mechanisms and ensure that the cancer problems of minorities, the medically underserved, and persons age 65 and over are adequately addressed.

From 1976 to 1982, Dr. Sondik served as Chief, Program Analysis and Evaluation Branch, National Heart, Lung, and Blood Institute (NHLBI), NIH and Deputy Director, Office of Program Planning and Evaluation (NHLBI), NIH.

From 1970 to 1975, Dr. Sondik conducted research and taught at Stanford University in the Department of Engineering-Economic Systems with collaborative appointments in the School of Medicine and in the Department of Communications.

EDUCATION:

B.S. Electrical Engineering, University of Connecticut, 1963;
M.S. Electrical Engineering (Control Systems), University of Connecticut, 1965;
Ph.D.
Electrical Engineering, Stanford University, 1971.

PERSONAL:

b. August 14, 1941; US Citizenship

Married, two children (2/13/95)

OVERALL PROGRESS AGAINST CANCER

Mr. PORTER. Dr. Sondik, you are absolutely right that cancer touches almost all American families. Right now, at this very moment I have a woman who has been on my staff since I was elected to Congress. She is in the hospital with pneumonia and has been on chemotherapy and has done a bone marrow replacement. So it touches us all. It is a terrible and frightening disease.

Your predecessor, Dr. Broder, was quoted in the March issue of the Washingtonian as saying, "It is not appropriate for people to make a career out of saying that we are not making progress in the battle against cancer. It is likewise inappropriate for some scientists to issue promissory notes and brag about the glorious progress we are making."

I think it is difficult for people to assess where we are in the fight against cancer. Many people are alarmed about the increasing incidence of certain cancers like prostate and breast cancer. Yet an article in the February 1 issue of the Journal of the National Cancer Institute seems to downplay the increasing incidence saying that much of it can be linked to better detection or cigarette smoking.

The article notes that death rates are decreasing for most cancers, particularly for those under 65, and in an editorial accompanying the article even predicts the decline of cancer as an important health problem over the next 30 to 50 years.

I guess what I would like you to do is bottom-line this for me. I know you discussed this in your opening statement.

Where are we overall in our fight against cancer?

Dr. SONDIK. Certainly overall the trends are increasing quite fast in incidence and much less so in mortality.

Over the years, we have analyzed it in a variety of ways. For me, the way to analyze it is to look at each cancer separately and kind of peel each one off, if you will, like we are peeling the layers off an onion. The first one to look at I think is lung cancer.

LUNG CANCER

We are making progress against lung cancer from the prevention side because we are making progress against tobacco use. It has taken an enormous amount of time for this to happen. It goes back to 1964, the first Surgeon General's report.

For the first time, over the last couple of years we have seen a flattening in the mortality trend among men. We don't see that flattening of the trend among women. When we extrapolate, we can see that perhaps we will start seeing this trend turnaround in women, perhaps in the mid part of the next decade if not even later.

So in that sense, we have something positive. In fact, if we eliminate lung cancer from the picture and just look at overall cancer, we see that mortality rates have had a very slow decline. In fact, they have fallen perhaps 6 percent, if that, since 1973 without considering lung cancer. Including lung cancer, they have gone up about 6 percent.

Lung cancer is very important to the overall trend. There are some cancers for which we see a relatively steep decline in mortality and clearly we are pleased about that. But for some of them, we are not quite sure why this is happening. For example, stomach cancer is declining in the United States as it is all around the world, probably because of better nutrition and better refrigeration. Other cancers—bladder cancer, for example—have declined in mortality probably due to better treatment. On the other hand, we have non-Hodgkins lymphoma, which has had a steep increase not only due to AIDS, but in the upper age brackets as well, for reasons that aren't clear.

PROSTATE AND BREAST CANCER DETECTION

So I think the bottom line for me is that cancer is a problem that is changing relatively slowly. Some of the trends that are very rapid are due to factors that we can identify such as early detection for prostate cancer and again early detection, to a degree, for breast cancer. But early detection for breast cancer does not eliminate the problem by any means. There is an increase of about 1 percent a year that we can't explain in breast cancer. In over 30 years, that is a great increase.

One point I would like to make about prostate cancer is that a lot of the increase—up to 244,000 cases from 200,000 last year—is certainly due to the aggressive efforts at early detection. There is a component, as well, in prostate cancer that we think is not solely due to that early detection. But I think it is important to realize that every one of those cases detected is a case that will be dealt with by the health care system. In prostate cancer, we are dealing with a problem. Our knowledge of how to deal with it is incomplete.

PROSTATE CANCER TREATMENT

We know, for example, that in prostatectomies there will be a 1 percent mortality rate. It is not clear, as we know by surveying the literature and our knowledge at this point, just how prostate cancer should be treated. In fact, we have a trial underway that is comparing watchful waiting against intervention.

So I think it is important to realize that even if some of the increase in the incidence figures is due to early detection, each one of those figures is, in effect, a case that is going to be dealt with by the system. We will use health care resources and in fact could have negative outcomes for the people involved.

LONG TERM OUTLOOK

Mr. PORTER. Now the long-term.

Several weeks ago, six Nobel laureates addressed our panel. Dr. Michael Bishop stated in his testimony that for the first time in his 30 years as a biomedical scientist, he believes that we will eventually conquer cancer, even though it will take several more generations of hard work.

Do you want to comment on that prediction?

Dr. SONDIK. I was very pleased to read that. I am sorry I wasn't here to actually hear him say it.

I think that we have undergone an enormous change in our knowledge about cancer. I think that is clear from the beginning of the National Cancer Program to today. I think what we thought at the time about how we could address cancer and approach it and solve the problem—we realize that was naive. Today, though, I think we know enough about the underlying molecular biology of cancer—the structure of it, the relationship between factors that may influence the cell to go awry—this gives us a path to follow.

I don't see this problem being solved in the next decade, perhaps in the next 2 decades. But I think if we take the long-term, based on the knowledge we have built thus far, I think we can see a path to follow.

I am hopeful, but I am certainly not going to say that it is in the bag and it is clear what we need to do. But the paths that we can follow now look as if they are going to bear enormous fruit.

Mr. PORTER. Mrs. Lowey.

BREAST CANCER DETECTION

Mrs. LOWEY. Thank you very much, Mr. Chairman.

I thank you, Doctors, for being with us today. We appreciate all the very important work you are doing. As our Chairman said, there are very few of us who are not touched some way through family, friends, or neighbors with this horrible disease. I look forward to the day when we can truly eradicate it. I appreciate the important work that is being done.

As we all know, scientists recently discovered a gene for breast cancer. And in your testimony you state "Genetic endowment is not synonymous with destiny." The world of genetically-based disease is somewhat new to most Americans and we have been hearing from ethicists about whether we should or should not discuss it.

Could you explain to us in non-scientific terms what the discovery of the breast cancer gene actually tells us and what it does not tell us? I think women and families need to understand what it does and what it does not do to us. Could you explain?

Dr. SONDIK. I hope I can. That is a tall order for a discovery like this.

But as I see it, if one has this gene—this marker—it tells one that one's risk of developing cancer is much higher than it is for a person in the general population. It doesn't say to the individual that it is absolutely definite that you will develop cancer. It doesn't tell us at this point how best to deal with it. In fact, that is part of the research agenda. Part of the real challenge of the cancer research agenda over the next 10 to 20 years is how to incorporate these risk levels into the research that we do to particularize the research for these specific risk levels.

As I said, it doesn't say to the woman that she will definitely develop breast cancer. But it does give us at this point some clues as to what the individual might do to detect it early and at that point to deal with it as best as we can.

Mrs. LOWEY. Following up on that, in your justifications you mention the decrease in mortality rate from breast cancer and you say that the decline is not uniform across all female groups. However, you say that there is an improvement for white women and you give the various reasons for that. This is very important information. I think it is directly related to the decisions about informing women as to whether they have this gene.

What can we do to assure that all women have access to the information they need to prevent and treat breast cancer? We know, for example, that mammography is one of the few methods of prevention now in place. I am very interested in your work in magnetic resonance imaging. Where do you think MRI research could take us in our efforts to prevent progression of breast cancer? I am also interested in your relation with the Breast Cancer Action Plan. We have a lot of information. The mortality rate is going down slightly, but there are many people that still are not the recipients of this information, although there are many ways to prevent it.

Dr. SONDIK. I think it is important that I state that we believe that this gene is responsible for perhaps 5 percent of breast cancer. I think it is very important that the general population not feel that this gene can, in effect, predict their destiny. This is only applicable to a relatively small number of families who are afflicted with it.

INFORMATION DISSEMINATION

Your point about information is extremely important. We have a variety of mechanisms for communicating this information. I mentioned some in my testimony, including 1–800–4–CANCER, and the medical literature. We work with the American Cancer Society and other groups to assure that this information reaches as many people as possible.

I think one of the strategies that will help us in the future with this is the Secretary's Breast Cancer Action Plan. Two of the groups under that—one involving consumer input and the other involving information, in particular the information highway—I think will enable us in this public/private partnership to use as best as we can these avenues to communicate to the American public.

There has been a great deal of confusion about these issues. I think it is important that we try to get the facts out about all these issues—not only mammography but treatment as well—so that we present information in terms of the pros and the cons, if you will, so that women can make an informed decision. I think this is especially true in mammography.

BEHAVIOR MODIFICATION

Mrs. LOWEY. I am particularly concerned about behavior modification. We are aware that 70 percent of all cancers are related to lifestyle choices—diet, smoking, et cetera. I am wondering whether Americans are getting the information they need to change their behavior. We all read the "fat" labels on the boxes of cereal and other foods.

Number one, are they getting this information? Do you feel that we are really successful in changing behavior? In fact, you see a report about how smoking is going down and people are buying fat-free products, then the next day you see a report saying that the sale of hamburgers and steaks and fatty products are really going up.

So number one, are people getting the information? Have we been successful in changing behavior? I think that is what concerns you most about this gene. It is just 5 percent of the breast cancers. In fact, if people knew about it, there isn't much they can really do except change the behavior. In fact, if they're not changing behavior with the knowledge you are putting out there, what can we do more effectively to change that behavior?

Dr. SONDIK. Smoking I think illustrates how difficult it is to change behavior. The fact that we are making in-roads now in smoking and have for the past 10 years or so—but it took 20 or more years for us to see an impact—shows just how difficult it is to change a behavior that is related to preventing a disease.

MAMMOGRAPHY

Until relatively recently, many physicians were not recommending mammography to their patients. It is hard to believe, but in fact that was the case. For some reason, we were reaching women and the public, but we were not reaching those who actually have a major influence on what happens.

So we have taken this knowledge that we have gained from doing surveys and the like, and redoubled our efforts to disseminate this information in an effective way, again working with these different groups.

DIET MODIFICATION

Diet is an area that I am particularly interested in. As you know, the NCI cosponsors with industry the Five-a-Day program that was born in California and transferred to the entire country. We know from the surveys that accompany that program that people do understand. They have gained knowledge. There is no question about it. Yet when we look at the overall figures for change, the change is relatively small. We find that if in fact they buy low-fat in one area, they might go to high-fat in terms of desserts and the like. It is very, very difficult.

But I think one of the things we have to do is have realistic expectations as to how long it is going to take.

I was just at a meeting with Dr. Ernst Wynder, a champion of comprehensive school health education in the earliest years. He feels very strongly—and there are many who agree with him—that the time to change behavior with respect to diet and health behavior in general is in the earliest years. One can have a major impact then when the paths are actually set and the behaviors are really set. I must say that I tend to agree with that. I think the investment in children is absolutely essential.

Mrs. LOWEY. We have known that for a long time. This is nothing new. I know Dr. Wynder and I have been to the American Health Foundation. I have talked with him. I worked with Matilda Cuomo on the nutrition programs in the schools. This is really nothing new. Are we going to continue saying this for the next few years? Are we really changing behavior? Are we really getting these nutrition programs in the schools?

There are a lot of demonstrations around, but are we as a country making the kind of investments to truly change behavior? I know it is difficult, but I have been talking about this for 25 years or so, as you probably have.

Dr. SONDIK. I think we're making at best modest gains in changing dietary behavior, for example. I don't think you can say that we're doing more than that. But as I said, it takes time. We are trying to find more effective ways of doing it. But I also think we need realistic expectations as to how long it is going to take. If we let up, if you will, we will lose. But if we continue the education process and continue to make it profitable for those who deal in food, one way or another, to change toward healthier foods, then I think we will have progress.

Mrs. LOWEY. Am I out of time, Mr. Chairman?

Mr. PORTER. I'm afraid you are.

Mrs. LOWEY. Let me just say that I am a very strong supporter of any investments in prevention and nutrition research and behavioral modification. I would probably be your best subject because I haven't been very successful at it myself. Thank you very much.

Mr. PORTER. We will probably have time for a second round.

Mr. Wicker.

Mr. WICKER. Thank you, Mr. Chairman.

CANCER INCIDENCE

Do I understand you to say, Dr. Sondik, that cancer incidence is increasing in general, that in particular the incidence is increasing with regard to lung cancer and breast cancer, and that if it were not for those two types of cancer, the rate would be decreasing?

Dr. SONDIK. In terms of incidence, it is increasing. In terms of mortality, what we see is a slight turnaround in lung cancer among men. So the death rate is actually coming down among men. It has turned around for white women for breast cancer, but the incidence rate continues to increase for breast cancer.

Mr. WICKER. In what areas of cancer is the incidence decreasing?

Dr. SONDIK. It is decreasing rapidly for stomach cancer. The reason for that, as I said, could be attributed to improved nutrition and refrigeration.

There is a decrease—although not as much a one as we can achieve—in cervical cancer. That is not actually a decrease in the actual incidence of the disease. It is a decrease in detecting the disease in the malignant stage. That is because through Pap smears we can find the cancer at its earliest in situ stages and eliminate it. That is another one where there has been a decrease.

Mr. WICKER. I noticed that you didn't mention longevity as a possible factor in the increased incidence of cancer in our population. Would you comment on that? Is the fact that we are living longer a factor?

Dr. SONDIK. That is a very small factor.

Mr. WICKER. Really?

Dr. SONDIK. Yes.

The principal reasons for the increases are due in large part to factors that we don't understand. For example, non-Hodgkins lymphoma—for males under 50 there has been an enormous increase in non-Hodgkins lymphoma because of AIDS. For people over 50, there has been an increase for factors that aren't clear, probably factors that are affecting our immune system in some way. But the increased longevity affecting that is really a tiny factor.

Let me just mention that the rates I am giving you are corrected for the age distribution in the population. So we are looking at rates that take account of the changing age distribution of the population.

Mr. WICKER. What do you mean by that?

Dr. SONDIK. We clearly have many more people, for example, who are over 80. In fact, since 1980 we have probably doubled the population that is over 80 in this country. When we calculate these changes, we account for the increased number of people who are over 80 and adjust for that so that we look at rates over time. When we compare rates between 1972 and 1973, we do that on the basis of a standard population, having in effect, the same percentage of people who are over 80 today as were in 1973. This allows us to take out that factor when we analyze the change.

BREAST CANCER

Mr. WICKER. Let me ask you about breast cancer.

How many types of breast cancer are there? Is it just one? Or are there several types?

Dr. SONDIK. There are many different characteristics of breast cancer. I am not sure I would say that there were different types of breast cancer.

Dr. VARMUS. I am not sure we know the answer to that question at this point. Traditionally, the way to assess different types of breast cancer was by looking under the microscope at a tissue sample and looking at changes in the histopathology. By those criteria, one might identify a handful of breast cancers.

But as we learn more about the biochemical damage that has been done to the genes of a cancer cell, one can think about making a more precise definition of different kinds of cancers. So certain cancers might have mutations in certain genes and other cancers might have mutations in other genes. Those may be very significant differences that we are only now able to assess due to our increased knowledge of the genetic basis of cancer.

BREAST CANCER DETECTION

Mr. WICKER. If breast cancer is detected early, what is the survival prospect of the patient? What if you begin treatment right when it is first detectable?

Dr. SONDIK. If it is detected in its earliest stage, then the five year survival is over 90 percent. If it is detected where it has spread through the lymph nodes, then the five year survival decreases to the order of 60 percent. If the cancer is detected in the metastatic stage where it has spread beyond the breast and axillary nodes, then the five year survival is around 20 percent, if I recall the figures.

[CLERK'S NOTE.—Subsequent to the hearing, the five year survival rate once breast cancer has spread through the lymph nodes was corrected to 40 to 70 percent, and the five year survival rate once breast cancer has spread beyond the breast and axillary nodes was corrected to less than 10 percent.]

Mr. WICKER. So would it be fair to say that since the death rate is declining by only 5 percent over a 3-year period, we're still not detecting it quickly enough in a large percentage of the population?

Dr. SONDIK. There is no question that we still detect a significant fraction of cancer too late. There is no question about that.

Mr. WICKER. What would that fraction be?

Dr. SONDIK. I believe it is 20 percent of cases that are detected in the metastatic stage. I would have to check on that figure for the record, but I believe it is about that. Given the very low survival for these patients, these clearly are lives we could save if the cancer were detected earlier, or at least these are lives that could be prolonged.

[CLERK'S NOTE.—Subsequent to the hearings, the percent of cases detected in the metastatic stage was corrected to 7 percent.]

BREAST CANCER INCIDENCE

Mr. WICKER. Did you say that there is an increase in the incidence of breast cancer of 1 percent per year?

Dr. SONDIK. The increase has varied over time. Over last year, we have not seen a change of any significant proportion in the increase. But since about 1980, the increase has been about 2 to 3 percent per year. But we know that a significant portion of that—I would say 1 to 2 percent—was due to early detection. But underlying the early detection there is an increase we see when we go back to our earliest records. In fact, if we go back to records we have from the State of Connecticut—which has been collecting this data now for 50 years—we can see over time about a 1 percent change per year. It is that change to which I was referring to that we can't identify a particular cause.

BREAST CANCER CAUSATION

Mr. WICKER. Are you willing to speculate for me about the underlying cause?

Dr. SONDIK. To whatever extent I can.

Mr. WICKER. Yes?

Dr. SONDIK. I thought you were going to propose a hypothesis.

Mr. WICKER. No, I want you to propose. [Laughter.]

I am not smart enough.

Dr. SONDIK. Certainly one of the factors is diet. I feel diet is a very compelling factor in breast cancer. When we look at the international studies and we compare—as has happened comparing studies of Japanese living in Japan, Japanese living in Hawaii, Japanese living in California—and we see the sharply rising breast cancer rates among these groups as they have migrated from area to area, we look at the factors that could be involved. Diet continues to come out as a strong factor.

But if you ask me what specific component of the diet, it appears to have to do with fat, but we can't be more specific than that at this point. That is one of the reasons for the trial that is now underway, the Women's Health Initiative, which has reducing fat as one of its interventions to see if it can reduce the incidence of breast cancer.

But without the change in diet, over time we have an effect that is along the lines that we see in this increase in breast cancer incidence. In other words, a slow progressive increase over time.

There may also be other risk factors that we don't understand. For example, we know when we have compared mortality from breast cancer against the birth patterns of women—that is, when they have had their children, particularly their first full-term birth—we see a startling relationship between the fact that women who give birth at an earlier age—say, 20 or earlier—seem to have a protective effect against breast cancer compared with women who give birth later—say at 35 and beyond, or who never have children.

Those patterns of first full term birth clearly have changed over time. And we can see in the mortality figures a relationship between those patterns and mortality. In other words, when women were in fact having children earlier, we see a reduction subsequently in the breast cancer rate. That could also be having an effect.

The environment has been raised as a factor. That is one of the issues that is under evaluation now in the Long Island study and in other studies.

But what we have seen in over 30 years of intensive epidemiology study is that diet is playing a key role and that other factors play a role in breast cancer. But we still don't have the complete picture that explains this 1 percent increase per year.

Mr. WICKER. Thank you, Mr. Chairman.

Mr. PORTER. Thank you.

Mr. Bonilla.

LEUKEMIA TREATMENT RESEARCH

Mr. BONILLA. Thank you, Mr. Chairman.

Good morning, Dr. Sondik.

Dr. SONDIK. Good morning.

Mr. BONILLA. We often clip articles in our office because we are so interested in developments in cancer research. If you will bear with me, I am going to ask you about a couple we have seen in the past few days and weeks.

The first one was published last month on the "smart bomb" that kills just leukemia cells. It attacks and kills leukemia cells without harming normal cells, apparently. The article says that the technique might be tested on humans very soon—maybe even this summer. The smart bomb could also be used for some cancers in the breast, ovaries, and brain. What is your opinion of this research? Do you think we ought to be spending more time and effort on leukemia fighters like this?

Dr. SONDIK. Leukemia is a major killer. In fact, the overall 5 year survival of all leukemia combined is 35–40 percent and ten year survival is about 25 percent. What you will see in that article is something that in effect is at the cutting edge of biomedicine. I think it is important that we do this. And what we learn there can have an effect on other cancers as well.

Dr. CHABNER. I think you're referring to the article about a genistein link to antibody. That is an interesting area. It is a compound that interacts with a growth factor and signals that flow from the growth factor. The compound has been studied on its own, but linking it to an antibody directs it to the tumor cells. It is a very interesting idea.

There are a number of clinical experiments going on with monoclonal antibodies linked to all sorts of toxins and drugs. Thus far, there has been limited success. The one area in which there has been some very promising work has been in the treatment of lymphomas with an antibody called the B–1 antibody. It has been tagged with radioactive iodine and it has had some strikingly good results with certain kinds of lymphoma.

Other trials with monoclonal antibodies have been less successful. It is possible that this one will be more effective and there is a lot of interest in this. We are supporting a great deal of research directly related to this. Hopefully, we will have the trials to talk about next year.

These kinds of compounds do take some special work to get them into the clinic because there is always the problem that you may be, in man, affecting some vital organ or normal tissue. So you have to be careful about doing these experiments.

Mr. BONILLA. Understandably so, but this is certainly an exciting prospect.

Dr. CHABNER. A lot of research is going on in the clinic very closely related to this. This particular compound in this form is not yet in the clinic, but it will probably happen within the next year.

METASTASIS PREVENTION

Mr. BONILLA. Dr. Sondik, I have another one about pectin. Earlier this month researchers at the University of Michigan found that pectin can prevent the spread of prostate cancer. I was wondering if that was the same kind of pectin Grandma used to use to make jelly gel. I understand that this pectin slows the spread of cancer by keeping free-floating cancer cells from sticking to one another or to organs elsewhere in the body.

The article goes on to say that if we had a pill that prevented cancer from spreading, then about 90 percent of all cancers could be curable. What do you think of this research? If it is correct, could we prevent about 90 percent of cancer if we control the spreading? This was just earlier this month in a local newspaper.

Dr. SONDIK. Well, I have to admit that this is the first I have heard about the study. My colleagues may have heard of it. But in terms of the underlying statement about preventing the spread of cancer, I think that is an excellent point. What kills people from cancer is clearly the spread, the metastasis. If there were a way of preventing the metastasis, I think we would certainly be a major step ahead. I am not familiar with this article, but there is research underway on trying to understand exactly how a cancer metastasizes. There is research on angiogenesis, which has to do with the blood supply that a tumor has to have in order to grow. So if we can do that, it is one of the many paths toward treatment.

Mr. BONILLA. I will be glad to give you my copy.

Dr. SONDIK. Thank you. I clearly don't get the right journals. [Laughter.]

MELANOMA VACCINES

Mr. BONILLA. I have a question now about skin cancer. There was another item out recently about that.

Since 1980, the incidence of malignant melanoma, the most deadly form of skin cancer, has increased over 65 percent. You state in your budget justification that a vaccine containing MART–1 will be ready for clinical testing by the end of fiscal year 1995. What is the difference between MART–1; MCV, which is being developed at the John Wayne Cancer Institute; and acusite, which is being developed at the Oregon Health Sciences University?

Can you tell us about the differences and whether you think we are close to having a vaccine for this type of skin cancer?

Dr. SONDIK. Not being a clinician, I think I should turn that over to my clinician colleague.

Dr. CHABNER. In the last couple of years, research has been able to define specific antigens or proteins on the surface of melanoma cells that are relatively unique. They are not absolutely unique to melanomas. For example, the MAGE protein is found in testis as well as in melanoma cells. There are other antigens that are found only in melanoma and in the retina in the back of the eye.

The hope is that antibodies or vaccines will be able to recognize these proteins that are found on the surface of melanoma cells and that you can sensitize the patient or the host, build their immune response to these specific antigens, and cause the regression of the tumors. It is part of an effort to define very specific changes in cancer cells that are unique to cancer cells but are not found in normal tissues. These could be the basis of either antibodies or vaccines.

Melanoma happens to be the one tumor where perhaps the greatest progress has been made, but there are a number of other abnormalities that relate to oncogenes that are found in cancers. These are the subject of vaccine trials that are going on right now.

The MART antigen is the subject of a vaccine trial, which we hope to begin at NCI this year. The Surgery Branch is working on this.

The other thing you mentioned, the acusite—I think this involves a monoclonal antibody directed against another melanoma antigen. There is a lot of research going on and it is moving very rapidly. The question is, once you find these antigens and develop vaccines whether they will really work and whether they will be specific for the tumor. There is always the possibility that you could damage some normal tissue in the process and that would prevent it from being useful.

MELANOMA AND SUN EXPOSURE

Mr. BONILLA. Does the increase in the number of cases of skin cancer directly relate or not relate to the greater use of protective creams like sunscreens? I would think more people are using it.

Dr. CHABNER. I think there is a lot more sun exposure for various reasons. People love to get tanned and they are spending a lot of time in the sun. There is some question as to whether the creams we use really eliminate the important UV rays that cause cancer. Perhaps Dr. Varmus would like to comment about that.

Dr. SONDIK. There is a direct relationship between this increased sun exposure and skin cancer in general, non-melanoma skin cancer especially. In melanoma, while there is a very strong relationship, it is not a perfect relationship by any means. In fact, one of the things that is a real challenge here is understanding why melanoma appears in parts of the body that are rarely exposed to the sun.

Dr. CHABNER. It is usually in sun-exposed areas. And there has been some progress in understanding melanoma, too. This last year a gene has been identified that is abnormal in some families that develop melanoma. It is one of the regulatory genes in the cell cycle. And it is probable that there are multiple factors. Some are genetic and some related to exposure. These factors interplay to result in cancer, particularly in susceptible people.

Mr. BONILLA. Certainly, even if it is found in areas that are not exposed, it would have to cut back drastically if people were more careful.

Dr. CHABNER. But mostly it is found in sun-exposed areas. The majority of melanomas are found in sun-exposed areas, not all but the majority.

PHYTOCHEMICALS

Mr. BONILLA. I have a question now about another item, something that has been nicknamed "veggie pills" that could be the next nutritional rage, according to this article on cancer-fighting abilities. Could you briefly talk about the new popularity of these things? I believe they are called phytochemicals, which could help curb the growth of some cancer cells. I understand that these will be sold widely by chains such as Wal-Mart very soon.

Since only 10 percent of Americans eat five servings of fruits and vegetables a day, do you think these pills would actually help?

Dr. CHABNER. They have a plus side and a minus side. Clearly, there is a lot of epidemiology linking vegetable intake to incidence of cancer and vitamin C levels, for example. Vitamin A is known to have some cancer-preventing properties. However, this is a somewhat dangerous area, too, because some phytochemicals have estrogenic activity. There has been some concern that some of these naturally occurring compounds might be predisposing people, if taken in excessive amounts, to breast cancer.

So I think it is not an area that we well understand. I would like to know what is in them and whether they have any of these components that could cause problems.

Dr. SONDIK. We do have an extensive chemoprevention program in which we are looking at the various constituents in food and vitamins and other elements and seeking to understand the relationship between these and incidence of cancer. We have some studies, for example, on beta carotene in Finland that was reported on last year. Contrary to the wide-spread a priori belief, betacarotene did not show a reduction in cancer. We have had quite a positive trial that took place in China in an area where the population's nutrition was not particularly good, and where there is a high rate of esophageal cancer. There, using multivitamins, it was found that the incidence of cancer could be lowered dramatically.

So we are learning more and more about this. I think one has to be careful about the hype for these things and look for the research base. We are supporting that base.

Mr. BONILLA. Thank you very much. I know my time is up and I may have some more questions for the record. I would appreciate it if you all would answer those.

RELATIONSHIP BETWEEN CANCER AND AIDS RESEARCH

Mr. PORTER. Mr. Miller.

Mr. MILLER. Earlier this month Dr. Fauci was here. Dr. Fauci was justifying AIDS research in that AIDS research applies to a lot more areas. In other words, it has a lot more benefit than just AIDS itself.

Could you discuss the interrelationship between what you're doing with cancer and with AIDS and what benefits you may have received in this area of cancer research from AIDS research? It is not all totally compartmentalized.

Dr. SONDIK. At NCI, our AIDS research is primarily in the intramural program. We have a very small extramural or grant-related program related to AIDS. And in the intramural program, we have a great complementarity between what we are doing in cancer and the AIDS research. Examples of this have to do with the tests that were developed in the NCI program to safeguard the blood supply, for example. I don't believe that could have taken place without the research in NCI on cancer and understanding retroviruses. We have the drug testing that has gone on. For example, the early work on AZT was accomplished in NCI.

The AIDS research program uses resources that were naturally developed for dealing with cancer. This is a very natural extension for them. But there is also the fact that AIDS is related to malignancies. What we learn in dealing with AIDS-related malignancies will really help us in dealing with malignancies in general.

So it is very difficult, in my view, to compartmentalize the research into an activity that will deal solely with AIDS and an activity that will deal solely with cancer. In fact, one of the points I made in my earlier testimony was that in one of the pieces of research in which we are examining the blood supply to tumors, part of the research we are using there comes from results that came from cardiovascular research. So there is a base that really cuts across all of biomedicine. One doesn't know exactly where one is going to have a result.

But I think there is a great similarity or complementarity between AIDS and cancer. What we learn in one clearly reinforces the other. The more we learn about the molecular biology of cancer, this becomes clearer.

TREATING TUMORS WITH BORON

Mr. MILLER. I had a constituent in my district in Charlotte County that corresponded about neutrons. There is some equipment—are you familiar with what I am talking about? This person ended up going to Japan for treatment. I am surprised that I haven't heard much about it for the past year or so. Can you give me an update on where that stands?

Dr. CHABNER. We have been very involved in this story. Some researchers in Japan have undertaken some relatively limited trials of boron-containing compounds. It turns out if you irradiate the element boron with very soft neutron radiation, or low-energy neutron irradiation, it gives off particles which are very destructive. Potentially, if you could get boron to attach to a tumor specifically and then irradiate it externally, you could kill that tumor and kill very little else because the idea is that you would find a way of localizing the boron to the tumor.

That is the big problem. Up to this point, no good method has been developed for specifically localizing the boron to the tumor so that you could irradiate it without damaging normal tissue. Several compounds have been proposed and there is actually a very limited clinical trial going on in the United States using the Brookhaven atomic energy facility. There was a proposal to turn one of the atomic energy facilities in Idaho—the Powerburst facility—into a boron capture experimental station. It turned out to be a very difficult location. It is not near any major population area, there are no hospitals in the area, so it was really an impractical proposal.

We are supporting a fair amount of grant research in this area. The major thrust of this research is to try to find better compounds that localize the tumors in carrying boron to the tumors. Some of the ideas are using monoclonal antibodies or using compounds that are specifically taken up by tumors like melanoma—tyrosine compounds.

There is a fair amount of research going on. It is an interesting theoretical idea, but it has some very practical limitations right now. There are anecdotal cases that have been reported. People talk about patients treated in Japan who have supposedly gotten better. But there are a very few cases and they are very difficult to evaluate. They are not treated under the same kinds of conditions we would treat an experimental patient here. So we have limited information about them.

Mr. MILLER. Do you have a report on the status of that? I have had a lot of correspondence with one particular constituent.

Dr. CHABNER. Probably the same person who has been writing to us. [Laughter.]

Mr. MILLER. I think he wrote a book about his wife's experience.

Dr. CHABNER. Yes, I know the case.

Mr. MILLER. Thank you very much.

[The information follows:]

Boron Neutron Capture Therapy

Boron Neutron Capture Therapy (BNCT) is an experimental modality for the treatment of cancer proposed as a means for selective irradiation of tumor tissue with sparing of surrounding normal tissues. The therapy has been under development for over 30 years, initially in the United States in the 1950s, then most prominently in Japan from the mid-1960s through the present, and most recently again in laboratories in the U.S. and elsewhere. BNCT is a two-component system composed on the one hand of a boron-containing compound that is delivered to the patient by the intravenous route, and which theoretically is capable of selectively concentrating in cancer cells with minimal concentration in normal cells, and on the other hand of low-energy thermal neutrons delivered to the area of known tumor by an external beam radiation device. The low-energy, or "slow," neutrons are incapable of damaging normal or cancer tissue unless the neutron encounters a boron atom. When the stable isotope boron-10 is irradiated with low-energy thermal neutrons, a neutron is "captured" by the boron nucleus resulting in a nuclear reaction with the release of high-energy alpha particles and lithium ions capable of destroying cells a very short distance from the site of the nuclear capture reaction (one or two cell diameters distant). BNCT is thus a binary system, each component of which is non-tumoricidal and non-toxic but when combined has the potential to be therapeutic. For BNCT to be therapeutically useful, the boron delivery compound must be capable of delivering a critical amount of boron to the tumor while avoiding surrounding normal tissue, and neutron irradiation device must be capable of delivering a critical flux of low-energy neutrons to the entire tumor. Modern technology appears to have solved most of the problems of neutron delivery to even deep-seated tumors. However, the boron delivery compounds used in all the early BNCT trials were incapable of selective concentration within tumor. Newer boron delivery compounds appear to be improvements over the first generation compounds, but it is still not clear that selective delivery has been achieved.

To briefly recapitulate the history of BNCT, in the 1950s about 50 patients with glioblastoma multiforme, a highly malignant brain tumor, were treated at Brookhaven National Laboratory and the Massachusetts Institute of Technology, using a boron delivery compound called BSH (sodium borocaptate) and a nuclear reactor to irradiate with slow neutrons. Unfortunately, no therapeutic benefit to patients was observed in terms of improved survival or improved neurologic status of patients, and the radiation toxicity was unacceptably high. In this country, BNCT clinical trials were halted while research to find better boron delivery compounds with improved tumor specificity and tumor retention characteristics continued. In the meanwhile, Dr. Hiroshi Hatanaka, who had been a neurosurgical fellow at the Massachusetts General Hospital and had worked with Dr. William Sweet in the U.S. BNCT trial, returned to Japan in the mid-1960s and began to treat patients, primarily with various types of brain tumors, using BSH as the boron delivery compound. These studies continued until Dr. Hatanaka's death in 1994 and about 120 patients were treated over a 25 year period. Review of these studies reveal that in general the results are not different from those expected with conventional external beam irradiation of similar patients. However, the Japan group has reported in symposia and has published in non-peer-reviewed book chapter format the analysis of small numbers of patients selected from the overall cohort, which suggests that some of these patients may have prolonged survival. These results have not been widely accepted as validating BNCT for the following reasons: (1) the analyzed cohort represents only about one-tenth of all patients treated and was selected from the larger cohort by rather idiosyncratic criteria; (2) the follow-up time for these patients was quite brief at the time of reporting, rendering the statistical analysis questionable; and (3) the pathologic diagnoses were not confirmed in every case. One widely publicized case from Dr. Hatanaka's studies, a patient who testified to Congress in 1993 about the perceived benefits she had received from BNCT for her "glioblastoma multiforme," subsequently died from progressive brain tumor and was found at autopsy to have a malignant central nervous system lymphoma, a tumor that is probably best treated with systemic chemotherapy with or without conventional external beam irradiation.

Preclinical research on BNCT in the United States over the past several years has been funded by the Department of Energy, and to a lesser extent, the NCI. The NCI has funded research focused on the development of improved boron delivery compounds. One compound, boronophenylalanine (BPA), has undergone extensive preclinical testing and has been used in patients with cutaneous melanomas in Japan. BPA is superior to BSH in tumor selectivity in animal tumor models and appears to be promising for the treatment of patients; however, it does not appear to have optimal pharmaceutical characteristics, and it remains to be seen whether the critical minimal amount of selective tumor uptake of boron in humans with cancer can be achieved. A number of other boron compounds have been synthesized with NCI grant support and some of these are in early stages of preclinical testing. One of these compounds, a porphyrin derivative, appears to have dramatic specificity for tumor tissue.

In September 1994 the first patient to be treated with BNCT in the U.S. in almost 35 years was treated at the Brookhaven National Laboratory with DOE support. She was treated for glioblastoma multiforme using the BPA compound. A second patient was treated in February 1995. In April 1995, both patients continue to do well. The NCI agreed to share with DOE the cost of synthesis and formulation of clinical grade BPA for this trial.

Thus, BNCT is a theoretically attractive approach to cancer therapy, but it has heretofore failed to demonstrate any superiority to conventional external beam radiation approaches for any tumor type. Its limitation so far has been the failure of boron delivery compounds to achieve the critical minimum mass of boron in the tumor cells while avoiding surrounding normal cells. This is a common cancer drug development problem, and one which has never been optimally solved for any drug type. (All effective anticancer drugs depend on biological differences between cancer cells and normal cells for their therapeutic advantage, not on the selective ability of the drug to be delivered to or taken up by the cancer cell.)

BIOGRAPHY

Mr. PORTER. Thank you, Mr. Miller.

Dr. Sondik, I have a curiosity question. How did an electrical engineer, one with a Ph.D. in electrical engineering, find his way into biomedical research?

Dr. SONDIK. Actually, it was quite straightforward. When I was doing my graduate work, I was on a joint project with the Stanford Medical School. The project had to do with two new areas of research then in Heart, Lung, and Blood. One had to do with a clinical trial that was being designed to reduce cholesterol to see if it reduced mortality. The second area had to do with a study called the Three Community Study, which was the first large study in communities to see if behavior could be changed with respect to diet and smoking and blood pressure, the principal cardiovascular risk factor.

My area of electrical engineering had to do with mathematics and operations research in mathematical modeling and statistics. I was particularly taken with both of these and the usefulness to applying mathematical models to both of these studies. All of these large-scale trials are not typical laboratory research in the sense that if something is done in Dr. Varmus' laboratory, for example, it will be repeated again in Dr. Chabner's laboratory.

These large-scale trials we really do them only once. They have to be designed in such a way such that they have the greatest impact possible on public policy and on science, of course. I was interested in that aspect. In terms of the behavior change study there was quite a bit of mathematical modelling involved in developing the design for the Three Community Study and in evaluating it.

That led me to come back to NIH and my path was set, so to speak, at that point.

Mr. PORTER. So from then on you were a biomedical researcher?

Dr. SONDIK. I suppose that is true.

STATE OF THE INSTITUTE

Mr. PORTER. Those were the easy questions. Now for the hard questions.

Some recent press accounts have depicted your Institute as an organization in turmoil beset by the departure of high-ranking scientists constrained by limited resources and anxious about an external review that is underway. We are certainly ready to believe that the press has exaggerated the situation, but I wonder if you can give us your impression as to the mental health of your Institute and what steps you plan to take to enhance stability and morale.

Dr. SONDIK. I think the last few years have been difficult for the staff because I think we have been preoccupied with several issues. But I think those issues are being resolved. I believe now that we really are on a path toward a more stable situation. I think the blue ribbon committee that is evaluating the intramural program is going to give very valuable suggestions that the staff is actually quite excited to see.

We have a very large portion of the staff involved in the Department's streamlining efforts for NCI, looking at what we do and how we do it to see if we can do it more effectively and more efficiently. I think we await a new Director in a very positive way, looking toward a new vision for the Institute.

I think the mental health of the Institute—and of course, I may be a little biased here—is pretty good at this point. We have a number of holes in the superstructure. In large part, we have these because of retirements that have come along naturally. The great growth in the Institute occurred some 20 to 30 years ago. We are at a time at this point that many people are going to think of other pastures. In fact, Dr. Chabner is here on his next-to-last day. He is retiring and moving to Boston.

So I think too much can be taken of the departures we have seen. But I won't say that all has been easy over the last few years. I do feel that we are on a very good path toward stability. I think the mental health of the place is pretty good at this point.

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT

Mr. PORTER. Last year, when Dr. Broder appeared before us, the National Surgical Adjuvant Breast and Bowel Project at Pittsburgh was very much in the news. At the time, Dr. Broder was beginning to take steps to deal with the Pittsburgh situation and to enhance the monitoring of your other clinical projects.

Can you briefly describe the actions you have taken to correct deficiencies in your clinical trials process? Can we now close the door on the entire Pittsburgh situation?

Dr. SONDIK. I think we can almost close the door on it. I am very positive about this. In fact, I went to speak to the National Surgical Adjuvant Breast and Bowel Project just a few weeks ago. I am pleased to say that Dr. Fisher has been appointed as the scientific director of the NSABP. The NSABP has been reorganized into two grants. They will be recompeting their grants starting this summer.

We have taken steps to increase the monitoring throughout the clinical trials within the Institute. We have done that through creating a branch. But we have done it even more so by talking with all the clinical trials. I think some of the fallout from this has actually been very positive. I think it has awakened people who needed to be awakened to the importance of this monitoring, to the need to communicate to the Institute and to the public as rapidly as possible.

Perhaps the only chapter that is not written at this point is the publication of the results that go back to the tainted data from Canada. I am pleased to say that papers on that have been prepared and are now in peer review by one of the journals. So I expect that this will be resolved relatively soon.

Dr. CHABNER. A couple of points about this are important. At the time this happened, there was some uncertainty as to how solid the most important trials were. We have gone back and audited the primary records on about 85 percent of the major trial, all the major contributors. Even though the trial was almost 20 years old at this point, 90 percent of the data was recovered and was accurate and there were not other instances where there was any suggestion of fraud or misconduct. We have participated in some serious scrutiny of the monitoring procedures for NSABP and have found that their site visits are now conducted very effectively and are finding no other instances where there is any suggestion of misconduct.

In general, this episode has heightened the requirements and the oversight and quality control for trials. The result has not been any further concern or any other episodes of fraud or misconduct. We feel that the clinical trials apparatus is in very good shape.

The downside of this is that it takes money away from doing research, money that could be spent on research itself. We really have to try to strike a balance between oversight and quality control and doing the research itself.

APPOINTMENT OF NEW DIRECTORS

Mr. PORTER. Dr. Varmus, when do you expect to name a new permanent director of the National Cancer Institute? We have heard that you have a very ambitious schedule, but given the fact that we are on the second year of acting directors for several of the Institutes, is it realistic to think that you can finalize the choice for the National Cancer Institute very quickly? Finally, does the law require you to go through a different process for the National Cancer Institute directorship than for other positions on the campus?

Dr. VARMUS. Yes, the schedule is ambitious, but I expect to fulfill it. The Secretary and I are meeting today with Phil Lee to discuss the results of the search, which we have completed. We expect to forward one or more names to the White House as early as tomorrow.

As you know, the appointment is made officially by the White House. It does not require Senate confirmation. So there are some differences in the way the search is conducted. It was conducted through a committee chaired by Dr. Paul Marks of Memorial Sloan-Kettering and composed of a large number of distinguished investigators and public members. The committee worked extremely rapidly and very hard surveying a large number of potential candidates. The candidates were narrowed to a moderate-sized list, interviewed, and names forwarded to the Department. We have conducted interviews and will be sending one or more names to the White House for final consideration this week.

Mr. PORTER. GMS and NIAMS both have acting directors also. Can you bring us up to date on where you are there?

Dr. VARMUS. The acting director for GMS—Dr. Marvin Cassman has been acting, as you know, for over a year. We have no plans at this point to institute a search for a permanent director. The search for a new director of NIAMS has been completed and I expect to have the names of the top candidates forwarded to me for interviews by me and others in Building One in the next few days.

Mr. PORTER. Thank you, Dr. Varmus.

Mrs. Lowey.

LONG ISLAND BREAST CANCER STUDY

Mrs. LOWEY. Thank you, Mr. Chairman.

Mention was made before about the Long Island Breast Cancer Study. Of course, I am very pleased that the National Cancer Institute in conjunction with NIEHS is moving forward with this study.

We are optimistic that the study will provide important insights between inherited genetic patterns and the environment.

Are you putting in place a mechanism to assure that new insights gained from the Long Island Breast Cancer Study will rapidly translate into clinical and community interventions that will make a difference to women?

Dr. SONDIK. First, of course, we have the usual mechanisms of publication and the like. But I think the National Breast Cancer Action Plan, again, is something that bridges the research to the public. In fact, one of the groups that has been formed under that has to with etiology. That group is taking into account the Long Island study when it makes its recommendations on how to use the Breast Cancer Action Plan monies. The group is very concerned about communicating to the public what it is we know at this point and what we will know. So this is an issue they will take up—rapid communication.

We also have been concerned about information and communication with the public on Long Island and elsewhere. We have set up a special liaison office, which is very unusual for us to do. But this is something that has worked out very well for this study. I could see this as being a model for a complex study that involves many institutions at the same time and has so many different questions it is trying to answer.

What we learn from this study will be important, but the methodology that is being developed to deal with this to measure these environmental influences, the analytic methods, the mapping of Long Island in terms of the various exposures—all of that is very important and I can see it being applied elsewhere. The rapid translation of this to other parts of the country I think are very important.

COLON CANCER DETECTION

Mrs. LOWEY. I am pleased to hear that. My colleague, Ms. Pelosi, couldn't be here today, but I know she is very concerned about the rapid increase in cases in the San Francisco area. I am sure, unfortunately, that other areas are catching up, too. So I thank you very much.

With regard to colon cancer, just recently it seems I have heard a number of cases where x-rays and procedures that are usually in place to detect colon cancer were just not accurately read and diagnosed by the physicians. Are there any advances in detection of colon cancer?

I would dare say that I am interested in that in other forms of cancer. These were horror stories where—in fact, the two people at well-known teaching hospitals in New York were being treated for diarrhea and all kinds of other symptoms when actually they had a polyp that was then diagnosed 2 years later as being cancer.

Dr. SONDIK. Dr. Chabner may want to speak to the diagnosis, specifically.

Over the last year—I think it is now about a year ago—we had the results of a clinical trial of detection of fecal occult blood test that showed that that test was very effective in reducing mortality from colorectal cancer. That, of course, is the first step in detecting it. We know that regular sigmoidoscopy is important, although we don't know the frequency at this point. Almost all experts recommend regular sigmoidoscopy or colonoscopy. But again, the frequency isn't clear.

But in terms of advances specific to diagnosis, I don't know of anything else, although Dr. Chabner may want to speak to that.

There is an interesting project that was presented to the National Cancer Advisory Board several months ago, something called virtual colonoscopy which involves the use of computer techniques and the MRI to visualize the colon using MRI and then computer techniques to reconstruct the series of images—slices, if you will—through the colon into an image that can be read by a physician looking for lesions of one sort or another. That is still at its very earliest stage but represents a different type of approach that one might take.

Would you care to make any comments?

Dr. CHABNER. I will just mention a couple of diagnostic procedures and then maybe Dr. Varmus will want to speak about genetics.

In imaging, there hasn't really been any major advances. It still depends on the skill of the person who reads the x-rays. The alternative to imaging is colonoscopy, which is a very effective thing if done expertly. It is expensive. It is usually reserved for people that are at higher risk or an older population where the risk is higher above age 50.

Colon cancer is a hereditary disease, like breast cancer. There is at least a component that is hereditary. In the last year, there has been a major advance in identifying the genetic lesion that is underlying some of these inherited cases. In contradistinction to breast cancer, there is a somewhat similar genetic test that could be done on a wider scale now and is widely available.

Maybe Dr. Varmus would like to comment.

Dr. VARMUS. I will simply point out, Mrs. Lowey, that there are two forms of colon cancer that can now be presaged by identification of inherited genetic abnormalities. One is called hereditary non-polyposis colon cancer and the other is familial adenomatosis.

It is possible now to make a risk assessment by using genetic techniques. These are not generally available and our belief is that they should not be generally available until we know more about how they can be used responsibly. But certainly in families where there is a history of colon cancer, it is possible to identify family Members who are at high risk. As Dr. Chabner has pointed out, we do have a very useful diagnostic procedure—colonoscopy—to look for early lesions and to carry out curative maneuvers.

Mr. PORTER. Thank you. We're going to try to finish here in 5 minutes because we have the National Center for Research Resources to cover also.

Mr. Bonilla.

BREAST CANCER RESEARCH FUNDING

Mr. BONILLA. Thank you, Mr. Chairman.

Dr. Sondik, I have a couple of brief questions about funding and numbers.

Could you review briefly the funding status of the breast cancer research supported by NCI for fiscal year 1995?

Dr. SONDIK. We have a total of $313,000,000 for fiscal year 1995 and project that to be $345,000,000 for fiscal year 1996.

Mr. BONILLA. Doctor, during the past 5 years, how much has funding for breast cancer research increased?

Dr. SONDIK. For example, in fiscal year 1994, we had $267,000,000. In FY 1991 it was $92,000,000. This year it was $313,000,000. So the increase in fact from fiscal year 1993 to fiscal year 1996 has been about 30 percent. That increase is spread over the various areas from basic research to detection, epidemiology, prevention, treatment, and rehabilitation.

EARMARKS

Mr. BONILLA. Very good.

And my final question. Is it the policy of the Institute to support earmarks for different types of cancer research? Or would you prefer to just have it all lumped together and have you make the decisions?

Dr. SONDIK. Clearly, we would prefer the flexibility we have. But when you say that we make the decisions, I would like to think that the research community has a great deal to do with that and that peer review has a great deal to do with how these decisions are made.

To me, NCI as well as NIH is a marketplace of ideas. It is the constant evaluation of these ideas that help optimize the resource allocation. The more flexible we can be the more we can respond to the good ideas that are out there.

Mr. BONILLA. So in a more concise answer, would that be that you would like to have more latitude?

Dr. SONDIK. We love latitude. [Laughter.]

Mr. BONILLA. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Bonilla.

Mr. Miller.

Mr. MILLER. I have no further questions.

Mr. PORTER. Dr. Sondik, thank you for your good testimony this morning, your very forthright answers to all the questions we posed. Obviously, you helped educate us a great deal, and we appreciate your being here to testify and the fine job you are doing at NCI and for our country. Thank you very much.

[The following questions were submitted to be answered for the record:]

PROTON BEAM CONSTRUCTION

Mr. Porter: What is your 1995-1996 budget for proton beam construction and operation?

Dr. Sondik: In 1995 the NCI co-funded $5.7 million to Massachussetts General Hospital for proton beam construction and equipment. 1995 is the final year for co-funding for proton beam construction. In FY 1996 there are no funds requested for proton beam construction. There will be no operational costs associated with the proton beam project in 1995-1996.

CONSTRUCTION FUNDS

Mr. Porter: Describe your anticipated use of $8 million in construction funds appropriated in 1995.

Dr. Sondik: The NCI's Construction Program supports the modernization, renovation and new construction of cancer facilities through the competitive award of grants to cancer research institutions located at universities and medical centers throughout the nation. In 1995, the NCI plans to award $8 million in construction funds. Massachussetts General Hospital will be awarded $5.7 million for the final phase of a Proton Beam Therapy facility.

The balance of the funds will be awarded through the competitive grant process to other institution(s) for specific cancer construction or renovation needs. In addition, funds will be provided to the Frederick Cancer Research and Development Center for the modernization, repair and improvement of facilities utilized in the conduct of cancer and AIDS research.

WOMEN AND INTRAMURAL RESEARCH AT NCI

Mr. Porter: An April 1994 report identified disparities in the treatment of women in your intramural research program. How have you addressed the findings of the report?

Dr. Sondik: The NCI has taken appropriate action to address the findings of the report you reference in Women in Science: Disparities Detailed in NCI Division (Science, vol. 264, April 1994). The Director of the Division of Cancer Biology and Diagnosis, Dr. Alan Rabson, discussed with his senior staff the data described in the article. I am happy to report that all agreed that special attention should be given to eliminate the apparent disparate treatment of women scientists in regard to resource allocations. Since the time of the report, Dr. Rabson's division has paid particular attention to resource allocations to assure that women scientists are not consciously or unconsciously subject to discrimination. I am pleased to inform you that as a result of Dr. Rabson's leadership in this area, the resource gap between men and women intramural scientist in his division has decreased each year over the past three years and we expect that gap to continue to narrow as we strive toward parity between the genders. Dr. Rabson and I, along with the other NCI Division

Directors, firmly believe that the quality of the research should be the determining factor on resource allocations without regard to the gender status of the scientist. The NCI will continue to monitor its progress in this area to assure gender equality in intramural resource allocation decisions.

ASSIST PROGRAM

Mr. Porter: Identify your 1994-1996 spending on the ASSIST tobacco control program. How does this compare to the expenditures of the State of California under its sales tax receipts program?

Dr. Sondik: Approximate expenditures by the State of California for tobacco control programs in that State was $60 million in 1994 and $55 million in 1995. These funds are part of the revenues collected by the State from excise taxes on cigarettes. The NCI budget for the 17-state ASSIST program is $22 million for FY 1994 and $24 million projected for both FY 1995 and 1996.

SPENDING ON VARIOUS CANCERS

Mr. Porter: Identify 1994-1996 spending for the following cancers: breast, cervical, prostate, ovarian, colorectal, lung, brain, liver, and pancreatic.

Dr. Sondik: The 1994 NCI funding for breast cancer was $267 million, the 1995 estimate is $313 million and the 1996 estimate is $345. Cervical cancer was $42 million in 1994 with an estimate in 1995 of $46 million and a 1996 estimate of $48 million. Prostate cancer funding in 1994 was $56 million, in 1995 the estimate is $59 million while the 1996 estimate increases to $61 million.

The 1994 level of funding for ovarian cancer was $34 million, while the 1995 and 1996 estimate is $39 million. In 1994 the NCI spent $83 million in colorectal cancer research and estimates funding $89 million in colorectal research in 1995 and $94 million in 1996. Lung cancer funding in 1994 was $106 million with an estimated funding level of $114 million in 1995 and $122 in 1996. The NCI funded $42 million in brain and central nervous system research in 1994 and estimates spending $43 million in 1995 and $44 million in 1996. Liver cancer research received a funding level of $38 million in 1994 and NCI estimates keeping that level of funding flat in 1995 and increasing to $40 million in 1996. The 1994 funding level for pancreatic cancer was $9 million in 1994 and is estimated to remain stable during 1995 and 1996.

SCREENING TESTS FOR BRCA-1 MUTATIONS

Mr. Porter: I know the NCI community felt great excitement at the discovery of the BRCA-1 gene. Since the discovery, however, press reports have cautioned that the gene is very large and complex, making a screening test quite difficult to develop. Will it be several years before any screening is available for high-risk women?

Dr. Sondik: Screening for BRCA-1 mutations in high-risk women who are members of known breast and ovarian cancer families is currently possible in a research setting. Available technologies, although labor intensive and slow, are adequate for identifying the causative BRCA-1 mutation in these high-risk families. Identification of a BRCA-1 mutation in one individual, facilitates screening of other family members to determine if they carry the BRCA-1 mutation and are at high risk of developing breast and ovarian cancer. Within the next few years, automated DNA-based technologies currently in development should make it possible to screen for mutations anywhere in the BRCA-1 gene using a single assay. Until such techniques are available, routine evaluation of the BRCA-1 gene in individuals or members of suspected breast cancer families is not possible in the clinical setting. Furthermore, rigorous clinical trials are necessary before a screening test can be made available to the public. Additionally, it is important to recognize that while a screening test may improve the diagnosis of genetic susceptibility to breast cancer, it is not a treatment.

MAMMOGRAPHY GUIDELINES

Mr. Porter: One of the storms your Institute has weathered over the past year is the controversy over mammography guidelines for women in the 40-49 age bracket. I understand a January study reported in the Journal of the American Medical Association confirmed the NCI position that mammography did not significantly reduce mortality for women in that age group. But the American Medical Association and American Cancer Society haven't changed their stance. Is it fair to say that the medical community is still at a standoff on this issue? Does NCI have any plans to reconsider its recommendation?

Dr. Sondik: Clinical trials have provided unequivocal evidence that breast cancer screening of women 50-69 by mammography with and without breast physical examination can reduce breast cancer mortality. The effectiveness of screening to reduce breast cancer mortality in women 40-49 remains uncertain despite eight randomized trials to address the issue. This was the conclusion from the National Cancer Institute International Workshop in Breast Cancer Screening in February 1993.

The report of the NCI workshop written by a panel of non-Federal scientists, chaired by Dr. Suzanne Fletcher, Editor, Annals of Internal Medicine, summarized the state of the science as follows. For women aged 40-49 years, "it is clear that in the first 5-7 years after study entry, there is no reduction in mortality from breast cancer that can be attributed to screening. There is an uncertain and , if present, marginal reduction in mortality at about 10-12 years. Only one study - Health Insurance Plan (HIP)of New York Breast Cancer Screening Study - provided information on long-term effects beyond 12 years, and more information is needed."

Equivalent conclusions were drawn in 1993 by the International Union Against Cancer (UICC) and the European Society of Mastology (EUSOMA) upon review of the world's clinical trial data. The U.S. Preventive Services Task Force in 1994 also came to the same conclusion upon independent review of the data.

Kerlikowske, et al (JAMA, 1995:149-154) incorporated in a meta-analysis published data from the world's randomized controlled screening trials as well as published data from less definitive observational studies. They confirmed the NCI workshop report, concluding, "There is no reduction in breast cancer mortality in women aged 40-49 years after 7 to 9 years of follow-up. Screening mammography may be effective in reducing breast cancer mortality in women aged 40-49 years after 10-12 years of follow-up, but the same benefit could probably be achieved by beginning screening at menopause or 50 years of age."

Smart, et al (Cancer, 1995, vol. 75, #7: 1619-1626) also did a meta-analysis. Their analysis of the randomized controlled screening trials confirmed the NCI workshop and Kerlikowske reports, even when excluding the negative findings from the Canadian National Breast Screening Study (CNBSS). Smart, et.al. went further and by excluding CNBSS data, the largest block of clinical trial data for the age group in question, and adding unpublished data from two Swedish trials they calculated a statistically significant reduction in deaths for women aged 40 to 49. Such selective inclusion of data raises serious concerns regarding validity. Additionally, Smart, et al recognized in their discussion the possibility that the benefit estimated could be due to screening after the age of fifty among women who were 40-49 years of age at entry, but could not calculate this effect because they did not have access to detailed trial data.

The National Cancer Institute (NCI) seeks to obtain additional information from the world's clinical trials data regarding this critical public health question. To this end the Institute established, as recommended in the 1993 Workshop Report, an international collaboration among trial investigators on an overview analysis of relevant data from all eight trials. Individual data records, not merely summary statistics is the basis of the overview analysis. These data are available only through the trial investigators. The overview analysis team will hold its fourth meeting in the summer of 1995, when the main agenda item will be making final modifications and adjustments to the analysis protocol.

Short of the NCI's planned overview analysis, uncertainty regarding the effectiveness of screening women 40-49 years of age will persist. In light of this uncertainty, various organizations and groups in the U.S. will likely take different points of view on this issue.

RAS INHIBITORS

Mr. Porter: Dr. Sondik, Dr. Varmus mentioned earlier in our hearings a March 16th Wall Street Journal article that described a new class of drugs being developed by the pharmaceutical companies that would target the "ras" gene, which regulates cell growth. These drugs were described as potentially a major turning point in the war against cancer. What is your assessment of the potential of this approach? Is the "ras" gene the controlling mechanism in many types of cancer?

Dr. Sondik: In reference to the potential of the new class of drugs, namely the ras inhibitors, NCI has played a vital role in the development of these agents. Ras is an oncogene that is over expressed in colon, prostate, bladder, lung and brain cancers, and myeloid leukemias, perhaps in as many as 20-30 percent of all colon cancers and a quarter of lung cancers. A number of pharmaceutical houses are developing ras inhibitors. Essentially these agents would stop cell division in cancer cells. Many of the scientists involved privately and in pharmaceutical companies trained at NCI and did early work on ras at NCI. NCI continues to support fundamental work on ras inhibitors and to screen agents for ras inhibition on the NCI drug screen. We anticipate that tests for ras expression may be useful in screening for many cancers. In 1994, NCI spent $4,021,000 for research on ras and anticipates spending $4,400,000 on ras research in 1995. Ras appears to be an important controlling mechanism, but more research is needed to more fully understand its role in cancer. It is most certainly a very promising lead at the present time.

FCRDC INTRAMURAL RESEARCH

Mr. Porter: You have recently recompeted the contract for your intramural research program at Frederick, Maryland. I was struck by the fact that the contractor, largely as a result of the Frederick contract, makes the list of the 25 largest NIH grantees. Can you tell us why this intramural program is run by contract rather than with Federal employees, which is the more common NIH model?

Dr. Sondik: The Frederick Cancer Research and Development Center (NCI FCRDC) began operations under the authority of the National Cancer Institute (NCI) eight months after then-President Nixon announced in October 1971 that the former Biological Defense Research Laboratories at Fort Detrick, Maryland would "be converted into a leading center for cancer research." No Government positions were provided to staff the Center, so the National Cancer Institute initiated an extensive competition for operation and management of these laboratories as a Government-Owned Contractor-Operated (GOCO) center.

In fact, the GOCO operation provides greater flexibility than that of a federal, or other type contract operation. The GOCO concept relieves the Government of many administrative functions. and provides for the redirection of resources faster to follow new research leads. The time required to change scientific direction and focus is greatly reduced. In addition, the Government can add to its capabilities for specific needs through corporate/academic input (e.g., scientific expertise, legal services, and engineering services), thus eliminating the need to acquire such separately. It also allows for more flexibility in meeting personnel needs and speed in acquiring goods and services.

The FCRDC operation includes a separate award for a basic research program (Advanced BioScience Laboratories, Inc.). This contract complements the NCI Intramural research programs, investigating such diverse areas as macromolecular structure and function; activation and expression of oncogenes in cancer; mechanisms, evolution and control of transformation; identification and regulation of AIDS virus genes and proteins; and genetics of cell differentiation and development.

Some of the resource and technical support functions to NCI and NIH investigations provided by the Operations and Technical support contract (Science Applications International Corporation, Inc.) include: development, evaluation, and production of natural products for use as chemotherapeutic agents against cancer and AIDS; provision of research animal holding services; natural products and clinical sample repositories; chemical synthesis and analysis services; electron microscopy; clinical immunology; and pathology/histotechnology services.

DOD BREAST CANCER RESEARCH PROGRAM

Mr. Porter: Can you describe for us how the Defense Department is spending the $210 million in breast cancer research funding it received in 1993, and how it plans to spend the $150 million received in 1995?

Dr. Sondik: The Department of Defense Breast Cancer Research Program is the result of Congressional appropriations included in the Defense budgets: $210 million in FY 1993 and $30 million in FY 1994. The Congress has appropriated an additional $150 million in FY 1995 for the continuation of this program. At the request of the Army, the Institute of Medicine (IOM) convened a panel to make recommendations about structuring the new breast cancer research program. These recommendations emphasized the need to concentrate on three areas of research: (1) infrastructure enhancement, (2) training and recruitiment of new, young clinicians and other health care providers, and (3) research projects from established investigators who are new to the breast cancer field. In September 1993, the Army published an announcement to invite proposals to this program which resulted in 2,680 submissions. The Army then contracted with the American Institute of Biological Sciences to peer review these research proposals. Based on IOM recommendations, a second-tier review was also conducted by an Integration Panel of scientists, clinicians, health care providers and advocates. The Panel emphasized both scientific excellence and programmatic relevance in its funding recommendations. Based on its findings, the Army awarded a total of 433 grants and contracts in the following categories: 27 for infrastructure enhancement; 135 for training and recruitment; 266 for investigator-initiated research; and 5 combined training and research awards. Projects include new investigator awards and Innovative Development and Exploratory Awards (IDEA) designed to support high risk areas of research, along with traditional investigator-initiated proposals. It is anticipated that additional awards will be made in FY 1995.

Mr. Porter: To what extent has your Institute been involved in the development of DOD's research plans or in the review of its research proposals?

Dr. Sondik: The National Cancer Institute has been involved with several planning components of the Department of Defense Breast Cancer Research Program. The NCI participated in the development of the Institute of Medicine's 1993 report, *Strategies for Managing the Breast Cancer Research Program*, presented to the U.S. Army Medical Research and Development Command. The IOM's report recommended an investment strategy and a two-tiered peer review system: the first tier assessing scientific excellence, the second tier assessing programmatic relevance. Also, NCI staff served on the FY93/94 Integration Panel for the Breast Cancer Research Program which was established to ensure that programmatic objectives outlined in the IOM report would be met and that a focused, coherent research program would result.

CANCER CENTERS

Mr. Porter: In 1996, you intend to award 18 planning grants for cancer centers. Are you responding to pressures to spread cancer center funding more broadly geographically? Are you likely to have the resources to support a substantial number of new centers when those institutions receiving grants try to convert to full center grants?

Dr. Sondik: The Cancer Centers program is one of the Institute's highest priorities for support. It is through the Centers network that many cancer research findings are either developed or disseminated into communities across the country. Accordingly, an expansion of the number of Centers based on scientific peer review would be desirable.

Six P20 planning grantees are scheduled to compete for a Cancer Center Support Grant and full status as a Cancer Center in FY 1996. P20 planning grants compete with existing Centers for status as full Center grants and are selected according to merit (priority score). New centers could, therefore, be supported in place of existing Centers with poorer priority scores. In addition, possibly one or two Centers could be added to the program (instead of substituting for existing Centers) if sufficient cost savings are achieved from the on-going awards.

Not all P20 Planning grants convert to full Center status as a P30 Core grant. Many P20 grantee institutions do submit applications that are subject to the peer review process and compete with on-going Cancer Centers for funding. Although not all grantees compete successfully for a P30 award, the planning funds they receive provide a beneficial return since the institutions are able to leverage their federal resources with institutional funds resulting in a more coordinated cancer research effort.

The NCI recognizes that to convert all of the planning grants into full fledged Centers would require a considerable investment of resources. But, as stated previously, planning grant funds often provide the impetus for greater commitment to, and organization of, an institution's cancer research efforts.

NATURAL PRODUCTS SCREENING PROGRAM

Mr. Porter: I talked with Dr. Broder last year about the program you have underway to screen plant extracts and marine organisms from around the world as anti-cancer drugs. Your justification indicates you have tested 34,000 substances so far. Have you found any that you consider promising enough to test in clinical trials?

Dr. Sondik: Our screening system in collaboration with extramural investigators has examined extracts of terrestrial plants, marine invertebrates, algae, bacteria, fungi, and protozoa for potential novel anticancer agents. While none of the agents have advanced to clinical trial, many compounds derived from natural-product leads have been identified in the screen as promising enough to justify further preclinical development. Examples of plant products are Curcurbitacins E & I, a plant product isolated from the seeds of *Amaris* species. Several marine organisms have also yielded promising anti-cancer products. These include Jasplakinolide, from a Fiji sponge; Dolastatin 11 from a seahare; Halichondrin B from several sponge species; and Halomon from a Philippines alga, *Portieria hornemanii*. These and several other substances derived from the NCI screen are currently in the pre-clinical development pipe-line and it is anticipated that some will enter early clinical trials in the near future.

Curcurbitacins, Dolastatin 11 and Jasplakinolide are being studied for their ability to disrupt elements of the cell's "skeleton." Halichondrin is a material active against melanoma and ovarian cell lines. Halomon is active in renal cancer cell lines and has also shown activity against ovarian cancer cell lines. Work is continuing on the production of a reproducible source of the material for Halomon as well as on determining dose, route of administration and scheduling of dose.

Compounds from the screening endeavor that have shown anti-AIDS activity include the following plant products that are currently in advanced preclinical development:

- $^{+}$Calanolide A. Isolated from the leaves and twigs of a tree, *Calophyllum lanigerum*, collected in Sarawak, Malaysia.

- Costatolide. Now known as ¯calanolide B. Isolated from the latex of a tree, *Calophyllum teysmanii*, collected in Sarawak, Malaysia.
- Conocurvone. Isolated from a shrub, *Conospermum* species, collected in Western Australia.
- Michellamine B. Isolated from a vine, *Ancistrocladus korupensis*, collected in the Korup rainforest of Cameroon.
- Prostratin. Isolated from the wood of a Samoan tree, *Homalanthus nutans*.

There are also a number of natural product derived agents that are in advanced clinical testing, in late Phase I or early Phase II clinical testing or awaiting IND submission and approval. Though these are materials that have significant NCI involvement in either their discovery or development, none of them came directly through the current screening system. Many of these products date their discovery to the early 1970s and in some aspects overlap the screening process. Examples of these materials are Taxol, Camptothecin, Didemnin B, Bryostatin, Dolastatin 10, and Ecteinascidin 743.

Taxol is from the Pacific Yew and is now in clinical use for ovarian and breast cancer. Subject to further investigation, Taxol may also be indicated in many other neoplasms such as lung and bladder cancers. Camptothecin is from the Chinese tree, *C. acuminata*. Camptothecin is used in clinical trials in both this country and in Japan. Areas of investigation related to camptothecin are gastric cancer, non-Hodgkin's Lymphoma, colorectal cancer, kidney cancer and lung cancer. Didemnin B, from the marine tunicate, *Trididemnum solidum*, has been through many clinical trials. It is currently in trials in Canada as an agent against non-Hodgkin's Lymphoma. Bryostatin is from the marine bryozoan, *Bugula neritina*, and is currently in Phase II trials at Johns Hopkins Unviersity with possible applications in the treatment of melanoma, lymphoma and nephroma. Dolastatin 10 is derived from the marine mollusc, *Dolabella auricularia*, and is now entering Phase I studies. Dolastatin may eventually be used in treating melanoma and ovarian cancer.

CANCER CONTROL

Mr. Porter: Your authorizing statute has required you to spend an increasing proportion of your appropriation on cancer control activities -- 10% in 1996. You are requesting appropriations bill language to overturn this authority. Can you describe why this earmark is becoming a problem for you? How much would you plan to spend on cancer control if your bill language request were approved?

Dr. Sondik: The Congress established a separate authorization for Cancer Control over 20 years ago when it passed the National Cancer Act of 1971. In all subsequent reauthorizations of the Act, language had been included that provided for a separate funding statute for this area of research. Public Law 103-43, the NIH Revitalization Act of 1993, changed the language to reflect that a set percentage of the NCI budget be allocated to Cancer Control activities. This provision was initiated with the FY 1994 budget when Cancer Control was to be at least 7% of the total budget; it was increased to 9% for FY 1995 and to 10% in FY 1996 and subsequent years. The result is that funds currently available for Cancer Prevention and Control activities have increased to $222 million in FY 1996. This compares to a level of $105 million in FY 1993 and ,therefore, reflects a significant expansion in our research efforts in this area.

I do not believe this has been a problem, in large measure because the appropriations for the NCI were increased during this same time period. The level being requested will support high quality peer reviewed science and I expect that the $222 million would be directed to prevention and control initiatives even if the existing statute were not in place.

ABORTION AND BREAST CANCER

Mr. Porter: The issue of whether having an abortion increases the risk of breast cancer is raised from time to time. Could you tell us whether enough scientific evidence exists to make such a judgment? Also, could you describe the current data on whether the use of oral contraceptives increases the risk of breast cancer?

Dr. Sondik: There is not enough information at this time to establish whether abortion increases the risk of breast cancer in young women. Recent publications have examined various aspects of the question, and one recent article has shown an association between therapeutic abortions and breast cancer risk. Other studies have not confirmed this finding, however.

Oral contraceptives do not increase the risk of breast cancer overall. It has been firmly established that for women who have ever used oral contraceptives --the Pill --, including older past users, the lifetime risk of breast cancer does not increase. However, a small transient risk in young current users, similar to a small increased risk of breast cancer in pregnant women, has not been ruled out. The magnitude of such an effect appears to be so small that investigators from multiple research institutions in England and the United States are having to pool their data to seek the existence of such an effect. In the meantime, the National Institutes of Health continues to fund new studies looking at various aspects of the oral contraceptive/breast cancer risk issue.

NCI BREAST CANCER BUDGET

Mr. Obey: Dr. Sondik, the NIH budget office has supplied a table showing cancer spending throughout NIH from 1992 through 1996. This table shows cancer spending increasing by $383 million over the four year period or about 18 percent($2,165M to $2,549M). This percentage increase is roughly the same as the biomedical inflation rate so in real terms you have been frozen. During this same 4 year period, however, the portion of cancer spending devoted to breast cancer increased by $271 million leaving almost a ten percent cut in the purchasing power of your non-breast cancer work. What has been the impact of this shift of resources on your basic research and on other specific cancers?

Dr. Sondik: As you note, the NCI budget has been essentially level with inflation in biomedical research. Within this budget, the NCI's research agenda has reflected increased emphasis on breast cancer. We have structured the funding in breast cancer to cover a wide variety of initiatives and find that many questions of fundamental interest to breast cancer research have considerable overlapping and supporting relationships to other areas of cancer research. Breast cancer research crosses the full spectrum of basic, applied and developmental research.

In the last several years, basic research has shifted as a percent of the research budget from the previous levels of 49 to 50 percent of the budget to approximately 47 percent. This shift has occurred as we seek to promote translational research and to transfer knowledge gained in the laboratory to benefits to human populations.

Our research interests have focussed strongly on understanding the basic biology of breast cancer and on using this information to improve detecting, treating, and preventing cancer of the breast. This emphasis has also promoted research in environmental factors, genetics, hormonal influences, diet and a wide range of other topics. As with all biomedical research, gains and insights in one area often shed light on other areas. For example, breast cancer genetic research shows that there may be an association of heritable breast cancer and familial pattern in prostate cancer.

Mr. Obey: How do the success rates for breast cancer compare to other priority areas within the institute?

Dr. Sondik: Although we do not routinely track the success rates of our Research Project Grants by disease areas, during the recent years of growth in breast cancer funding we did complete two special analyses of the unfunded grants to determine the impact of the increased funding on the success of applicants for breast cancer research funds. In 1991, at the beginning of the growth trend in breast cancer research, the success rate for breast cancer grants was 36 percent compared to the success rate for all RPGs of 28 percent. In 1992, to increase our efforts in the breast cancer research field, we issued 11 Requests for Applications in areas related to breast cancer research. These RFAs generated an enthusiastic response from the scientific community. In fact, the response was so intense that although we doubled the number of grants funded in breast cancer, the raw number of applications tripled and thus the success rate for breast cancer RPGs fell to 25 percent. The overall RPG success rate was 32 percent. Now as the breast cancer field has become more established, we expect the rate of growth in the number of breast cancer applications to stabilize. Because breast cancer funding continues to grow as a proportion of the funds available for RPGS, we expect the success rate for breast cancer grants will be higher than the overall RPG success rate. The 1996 President's Budget will fund approximately 20 percent of all RPG applications eligible for funding. Within this, breast cancer grants are likely to be very successful at levels of 23 to 28 percent depending on the number of applications submitted.

BREAST CANCER FUNDING

Mr. Obey: How much discretion does the institute have in adjusting the breast cancer funding levels if you see an imbalance between different scientific opportunities?

Dr. Sondik: The NCI has the discretion to adjust funding to balance the scientific program as opportunities and needs arise. NCI selects grants in a three tiered process involving peer review and judgment of scientific merit, advice from the National Cancer Advisory Board, and the need for scientifically balanced programs. The estimate of $345 million for breast cancer funding in the 1996 President's Budget is a target established by the NCI and its advisors as the levels most appropriate to meet both national needs for controlling and curing breast cancer and to provide funding for solid scientific research.

Mr. Obey: Over the last several years the Committee has expressed its concern about the ability of the Institute to attract applications. The number being submitted was virtually identical for five or six years. Has this situation improved?

Dr. Sondik: NCI was initially concerned about our ability to adequately meet the very large targeted increases requested in breast cancer research. The situation has improved greatly in the past three years, however. Through a combination of Program Announcements and Request(s) for Applications (RFAs), the NCI has actively solicited applications which are specifically targeted towards breast cancer research. Response from the research community has consistently increased. In addition, knowledge of the availability of funds for breast cancer research has resulted in an increase in the number of investigator-initiated research proposals related to breast cancer.

BY-PASS BUDGET

Mr. Obey: Since original passage of the National Cancer Act, the Institute has been required to prepare and submit directly to the President a so-called by-pass budget. How much money is proposed for your institute in the by-pass budget for 1996 compared to last year and compared to the President's budget? (Note: The bypass calls for $3.640 M which is a 70% increase over 1995)

Dr. Sondik: The 1996 Budget Bypass request is $3.64 billion which represents a 70% increase over the FY 1995 appropriation of $2.14 billion. It is 62% higher than the FY 1996 President's Budget of $2.22 billion.

Mr. Obey: These by-pass budgets have become virtually meaningless in the last decade or so because the amounts recommended are so far above what is realistic. I know these documents have other uses internally at NCI but given where we are headed budget-wise over the next few years, does it make sense to continue the by-pass budget process?

Dr. Sondik: The National Cancer Institute is required, under the provisions of the original National Cancer Act of 1971 (P.L. 92-218 and subsequent reauthorizations) to prepare and submit an annual budget estimate directly to the President. The purpose of the Bypass Budget is to define NCI's professional needs in a scholarly fashion based solely on scientific considerations. The Bypass Budget narrative reflects the complexity of cancer investigation and provides an accurate sense of what is needed to hasten most progress and address the diverse and continuing challenges of cancer research.

The Bypass Budget is recognized by the Congress as the professional judgement of scientific opportunities in cancer research, as evidenced by the authorization levels for the National Cancer Institute for fiscal year 1994 included in the NIH Revitalization Act of 1993 (P.L. 103-43, sec. 403).

GENETIC DISCRIMINATION

Mr. Obey: Last week I discussed with Dr. Collins at the Genome Center my concerns about the misuse of genetic screening tests to discriminate against people by insurance companies and by employers. Dr. Collins was very positive that this issue was being addressed in a timely fashion. An article in the New York Times this last Monday, however, indicates that the process is really out of control. What is your view of this issue in terms of cancer screening tests?

Dr. Sondik: The National Cancer Institute shares your concern about the potential for genetic screening to be used for discriminatory purposes and agrees with the position taken by the National Center for Human Genome Research that genetic screening is in its research infancy and not appropriate for use by the public. Individuals who wish to participate in research studies involving genetic testing must be informed of these potential risks. There is clearly a need for safeguards to privacy for individuals at risk. The views of the National Cancer Institute are consistent with two recently published statements by the National Advisory Council for Human Genome Research and the American Society of Human Genetics. The most important recommendation is that at this time, genetic testing should be considered a research tool, useful only in high-risk families. An enormous amount of research must be completed before we understand the relationship of alterations to the genes and the onset of disease. Until we understand which changes are related to risk of developing disease, and which are only minor variants, the results are uninterpretable. Therefore, the use of these very preliminary test results for decisions by insurers or employers is inappropriate and unjustified. Furthermore, the impact of genetic knowledge on the individual is unknown, the health care public is inadequately trained to interpret and counsel patients about genetic risk outside the research setting, and further research is needed to identify additional risk factors for disease.

There is a major effort in the scientific community to establish guidelines for appropriate use of these laboratory tests. Appropriate use of these tests includes the interpretation of the test results, genetic counselling, and education about screening modalities and possible additional risk factors for the specific type of cancer.

The NCI has sought the advice of its various scientific advisory boards in this matter of genetic discrimination and we are working closely with other DHHS components, other agencies, and as part of the Secretary's Strategic Plan for Breast Cancer Research, to assure that our technologic capabilities do not outstrip the protection of individual rights. Some of our efforts are as follows: The National Breast Cancer Action Plan Working Group on Genetic Susceptibility has set up an Anti-Discrimination Subcommittee to make recommendations concerning this issue. These recommendations would be expected to benefit all individuals with genetic cancer predisposition, not only those families at risk for breast cancer. Multiple NIH institutes including the National Center for Human Genome Research, the National Cancer Institute, the National Institute of Mental Health, and the National Institute of Nursing Research have co-funded a request for application (RFA) to stimulate the extramural scientific community to investigate these issues in a carefully controlled research setting. The NCI will hold a workshop to address concerns of genetic screening for colorectal cancer on April 11, 1995.

As an outcome of its meeting on March 28, 1995, the President's Cancer Panel stated that "elucidation of the human genome in the absence of standardized public policy on information dissemination, education of the public and health care providers, confidentiality of genetic information and the availability of psychosocial support is an incentive to discrimination based on genetic predisposition. Prevention of genetically based discrimination will have to be addressed immediately at both the state and federal levels where insurance is regulated."

Health care reform or Federal and state legislation may help create a level playing field in which genetic screening information contributes to the health of the nation without compromising individual rights. The determination that the Americans with

Disabilities Act (ADA) includes genetic predisposition for a disease as a disability is the first step in eliminating the potential for genetic discrimination. We understand that the Equal Employment Opportunity Commission is about to issue guidelines to clarify who is covered under the ADA. Many more steps are needed to insure that genetic discrimination does not occur. However, the potential misuse of screening information should not be confused with the importance of genetic information and its contribution to the understanding of cancer and other diseases and the development of new therapeutic or preventive opportunities to alleviate human suffering at all levels.

Identification of a specific genetic mutation may mean that cancer as an outcome is a certainty. However, we may find that options such as prophylactic surgery may prevent the onset of disease. Presence of a mutation to the BRCA-1 gene indicates that there is an increased probability, approximately 85%, of a woman developing breast cancer during her lifetime. It does not mean that loss of a productive life is inevitable, but that screening and other preventive strategies including proper diet and exercise should be inculcated into individual lifestyles. It also means that longitudinal monitoring of health status in a structured research setting may lead to earlier detection and treatment which may prolong life and provide more opportunities to learn about the progression and onset of disease.

WAR ON CANCER

Mr. Stokes: Launched in the early 70s, the nation's war on cancer is nearly a quarter of century old. What were the four leading cancers when the war on cancer was launched, and what are they now?

Dr. Sondik: The four leading cancer sites based on the number of estimated new diagnoses in 1971 were the same as those estimated in 1995: colon/rectum, lung, breast and prostate cancer. The order of importance, however, has changed. In 1971, the estimated number of colon/rectal cancers was higher than that for lung cancer with breast cancer as third and prostate cancer as fourth. In 1995, the order is reversed: the estimates reflect that there will be more cases of prostate cancer than breast cancer with lung cancer as third and colon/rectum fourth.

AFRICAN-AMERICANS AND CANCER

Mr. Stokes: According to your opening statement, in the United States, this year over 1.2 million Americans will be diagnosed with cancer and 547,000 Americans will die of cancer. You go on to state that African Americans have higher incidence and death rates for cancer overall. Specifically, what is the extent of cancer in the African Americans?

Dr. Sondik: In 1992, the overall cancer incidence rate among African Americans was 458 per 100,000 compared to 413 per 100,000 for whites. It should be noted that this difference is due to the very high rate of cancer among African American males (636 per 100,000) compared to white males (512 per 100,000). African American females actually have a slightly lower cancer incidence rate (336 per 100,000) than white females (346 per 100,000).

FOUR LEADING CANCERS

Mr. Stokes: The Justification indicates that four cancers account for more than half of all cancer deaths: Breast, Prostate, Lung, and the combination of colon and rectal cancers. In women, what are the leading four cancers and what are they in men? What four cancers account for more than half of the cancer deaths in African Americans?

Dr. Sondik: The four leading types of cancer deaths in women are, in this order, lung, breast, colorectal, and ovarian. In men the four leading cancers are lung, prostate, colorectal-rectal, and pancreatic. The four leading cancers in African Americans are lung, prostate, breast, and colorectal.

CANCER SCREENING

Mr. Stokes: For some diseases, such as diabetes, many Americans are not aware that they have the disease. This is the case for nearly half of the estimated 14 million Americans with diabetes. Is there a similar problem with respect to cancer? For which major cancers should there be routine cancer screening and how often should that screening take place?

Dr. Sondik. Currently, there are no means to ascertain the number of individuals in the population who might have cancer and are unaware of it. Any estimates would be pure speculation. Cancer cells can be anywhere in the body, may never accumulate in sufficient numbers to threaten the health of the individual, and may be undetectable with current technology. It is suspected that cancer cells develop and are eradicated by the immune system throughout life. The important issue is whether cancers which will eventually become deadly in an individual can be detected and eradicated in time to spare the individual's life at acceptable risk and cost.

The NCI may issue statements of scientific evidence which can be used in guideline deliberations at other agencies whose mission is more appropriate to guideline development. The Agency for Health Care Policy Research has established a systematic, evidence based process for reviewing the science and developing screening guidelines.

The NCI does maintain the Physicians Data Query (PDQ) system, a computerized database of information relevant to cancer that is available to both the public and health professionals. Experts in the cancer disciplines are organized into editorial boards which periodically review emergent scientific results and incorporate them into statements of evidence regarding the effectiveness of cancer screening by organ site. These statements are available on-line and in hard copy to the public. They include not only a summary of evidence, but explanations of the strength of evidence and references to the source documents.

PDQ summary statements relevant to screening evidence are provided below. References cited in the actual PDQ database are not included below.

In 1995, an estimated 1,252,000 people in the United States will be diagnosed with cancer and 547,000 will die of this disease. How many of these deaths could have been avoided through screening? Estimates vary from 3-35%, depending on the criteria. Screening for breast and cervical cancer alone is projected to result in a 3% reduction in total cancer deaths.

In developing the cancer screening statements, the PDQ Screening Editorial Board used the following definitions:

- Screening is a means of accomplishing early detection of disease in asymptomatic people.
- Detection examinations, tests, or procedures used in screening are usually not diagnostic, but sort out persons suspicious for the presence of cancer from those who are not.
- Diagnosis is made following a work-up, a biopsy, or other tests in pursuing symptoms or positive detection procedures.

The purpose of this section is to present the explicit evidence-based approach to the development of the state-of-the-art screening statements and the associated assignment of levels of evidence.

The statements are based on various levels of published scientific evidence and collective clinical experience. The highest level of evidence is taken as mortality reduction in controlled, randomized clinical trials. The results of clinical studies, case-control studies, and clinical information were considered in formulating the statements. In addition, the incidence of cancer, stage distribution, treatment, survival rates, and mortality were considered. The statements are subject to modification as new evidence becomes available.

Two requirements must be met for screening to be useful:

(1) There must be a test or procedure that will detect cancers earlier and,
(2) There must be evidence that treatment at an earlier stage of disease will result in an improved outcome.

These requirements are necessary, but not sufficient to prove the efficacy of screening.

Observation is the most widely available examination for the detection of cancer. It is useful in identifying suspicious lesions in the skin, lip, mouth, larynx, external genitalia, and cervix. The second most available detection procedure is palpation. It is particularly valuable in detecting lumps, nodules, or tumors in the breast, mouth, salivary glands, thyroid, subcutaneous tissues, anus, rectum, prostate, testes, ovaries, and uterus and enlarged lymph nodes in the neck, axilla, or groin. Internal cancers require an extension of observation through endoscopes, x-rays, and ultrasound. Laboratory tests, such as the Pap smear, and occult blood testing of the feces have also proven helpful for some of these cancers.

However, concerns regarding effectiveness and yield play a particularly important role in decisions to screen for cancers not easily amenable to earlier detection through physical examination in asymptomatic individuals. The performance of these tests is usually measured in terms of sensitivity, specificity, and positive and negative predictive values.

There are some cancers where screening does not appear useful: those where no early detection tests exist, as in cancer of the pancreas; and in cancers with no apparent localized stage, as in leukemia.

The type, periodicity, and commencement of screening in high-risk populations for most cancers reflect the judgment of expert practitioners rather than evidence from scientifically-conducted tests. Some individuals are known to be at high risk for cancer, such as those with a strong family history of cancer (in two or more first-degree relatives). Physician judgment is needed in such circumstances to determine the most appropriate application of available screening methods. Prudence dictates increased vigilance in the higher-risk populations. This primarily means that the high-risk person is identified, is counseled appropriately, and regularly undergoes the screening procedures of known benefit.

The relation of stage to survival and mortality is the basis of clinical cancer management. It is the major factor in prognosis, in the determination of treatment, and in the evaluation of end results. In the 1940's, a generalized staging classification of localized, regional, and distant (LRD) was developed to show long-term trends, and it is still useful. In the more detailed TNM system, which has been periodically modified, the (T)umor size, the status of the lymph (N)odes, and the status of distant (M)etastases are also categorized. These elements are then grouped into Stages 0-IV according to their association with survival. Classification of cancer by prognostic factors has developed through the extensive study of thousands of cases followed for many years. As malignant tumors increase in size, they have a greater propensity to metastasize to regional lymph nodes and to distant sites. Stage has such a profound effect that all randomized treatment trials require the comparison of similar stages in evaluating differences in outcome. In the Health Insurance Plan (HIP) breast cancer randomized screening trial, the reductions in mortality have been shown to be partly due to shifts in stage. In other cancer sites, shifts in stage may also herald improved survival and decreased mortality, though stage shift alone does not establish benefit.

Mr. Stokes: What is the five year cancer survival rate for the general population? What is it for males and what is it for females? What is the five year cancer survival rate for African American males and what is it for African American females?

Dr. Sondik: Based on data collected through the Surveillance, Epidemiology and End Results program (SEER) from 1986-1991 the five year cancer survival rate for the general population is 56.0%. The survival rate for all males is 51.9% and for all females 60.0% The survival rate for African American males is 37.9% and for African American females 46.9%.

BREAST CANCER

Mr. Stokes: The Committee heard considerable testimony from agency and public witnesses alike emphasizing that the overall death rate for breast cancer in American women declined about 5 percent between 1989 and 1992, the largest short-term decline in four decades. For white women in the 30-50 age group, death rates from breast cancer fell 8 to 9 percent over the same time period. However, for African American women, the rate of death due to cancer increased 2.6 percent. To what extent will this information be used to help focus the direction of research?

Dr. Sondik: Researchers are poised to address factors that may be contributing to the disparate breast cancer death rates of white women and African-American women. NCI adheres to the NIH policy that members of minority groups be included as subjects in all NIH-supported clinical research projects. NCI strives to move research to clinical trials expeditiously, particularly breast cancer; and supports research identifying barriers to participation in clinical trials. NCI works closely with the community to identify and remove barriers to participation.

Tissue resources for research now include information on the minority status of the patient; some resources, such as the Cooperative Breast Cancer Tissue Registry, also include treatment and outcome data. Efforts are being made to further enhance the value of these resources by linkage with SEER minority databases. Thus, as research on the biological mechanisms of breast cancer susceptibility and disease progression continues, researchers will be able to include the factor of minority status in the analysis of variables contributing to differences in response to treatment in clinical trials and subsequent survival. The role of any inherent biological differences in tumors can then be evaluated in the context of external non-biological factors, such as access to health care, which may contribute to these observed differences in mortality.

BRCA-1 AND BRCA-2

Mr. Stokes: According to the Congressional justification, researchers have successfully isolated the breast cancer susceptibility genes, BRCA-1 and BRCA-2. What percentage of breast cancer is attributed to these genes?

Dr. Sondik: Early-onset breast and ovarian cancer families constitute 5 to 10% of all breast and ovarian cancer cases. Mutations in the BRCA-1 gene are estimated to underlie approximately half of these hereditary cancer families. The location of a second hereditary breast cancer gene, BRCA-2, which underlies a portion of the remaining hereditary breast cancer families, has been reported. Existence of a "BRCA-3" gene has also been suggested. Intensive investigations to identify these genes are ongoing.

Mr. Stokes: What is the significance of the BRCA-1 and BRCA-2 gene finding, and what opportunities will the finding allow the institute to further exploit? How much is included in the FY 1996 budget request to exploit these opportunities?

Dr. Sondik: Identification of the genes underlying these hereditary cancer families is very significant for it allows screening of women at high risk of disease. Characterization of a BRCA-1 mutation in one individual family member facilitates screening of other family members to determine if they carry the same BRCA-1 mutation. Currently the characterization of mutations in hereditary cancer families and the identification of family members at high risk of disease is only being carried out in a research setting. It is also significant that identification of these hereditary breast and ovarian cancer genes may identify genes that are causative in non-hereditary cancer as well. Recent studies have suggested a role for BRCA-1 in non-hereditary ovarian tumors.

The identification of the BRCA-1 and BRCA-2 genes will enable investigators to pursue many additional research questions. Extensive studies will be necessary to determine the level of risk associated with BRCA-1 or other breast and ovarian cancer susceptibility genes. In excess of 80 different mutations in the BRCA-1 gene have been reported to date. The level of risk associated with individual mutations in the BRCA-1 gene must be determined before it is possible to distinguish between mutations conferring high risk and minor variants. An enormous amount of research must also be completed to identify and characterize the BRCA-2 gene and other possible hereditary breast and ovarian cancer genes. Information about specific genetic alterations that predispose women to breast and other cancers will enhance the Women's Health Initiative by suggesting additional components that might be included in both the observational and the intervention arms. Specimens collected from women enrolled in this trial can be used for studies of prevalence of genetic alterations.

The FY 1996 budget request includes a total of $4.5 million to continue research on the BRCA-1 and BRCA-2 genes.

NATIONAL ACTION PLAN ON BREAST CANCER

Mr. Stokes: To what extent is the Institute involved in implementing the Secretary's National Action Plan on Breast Cancer, and how is the plan being used to help direct the focus of breast cancer research?

Dr. Sondik: NCI has been actively involved in implementing the Secretary's National Action Plan on Breast Cancer (NAPBC). At its June 1994 meeting, NAPBC identified six priority areas which merit emphasis, and NCI staff are serving as co-chairs of two of these areas (Biological Resource Bank and Breast Cancer Etiology). Shortly after the June meeting, the Deputy Director of NIH, Dr. Ruth Kirschstein, designated the NCI-chaired Inter-Agency Working Group on Breast and Gynecologic Cancer, to serve as the programmatic focal point for NIH for coordination of activities and dissemination of information regarding the Action Plan. As Acting Director of NCI I serve as a member of the NAPBC Executive Committee and Steering Committee (as does the Chairperson of the National Cancer Advisory Board) and as a liaison to the DHHS Coordinating Committee. NCI staff are working closely with the Office on Women's Health in developing concept statements, RFAs, and operating procedures for the review and management of all activities funded under the NAPBC.

The plan is being used to help direct the focus of research in breast cancer etiology by having identified four areas needing emphasis: chemicals and hormones, viruses, radiation, and lifestyle factors. Four groups of experts for these areas have been convened and meet periodically to evaluate ongoing research in these areas as well as to identify research needs and gaps. These groups will be making funding recommendations to the NAPBC Steering Committee for breast cancer etiology projects to be funded in FY 1995. In addition, they are planning several workshops which may result in RFAs for FY 1996 funding.

COLORECTAL AND PROSTATE CANCER

Mr. Stokes: In your opening statement, you state that "we see fewer deaths from colorectal cancer, but more deaths from prostate cancers." How many Americans die from prostate cancer, as opposed to how many Americans die from colorectal cancer?

Dr. Sondik: It is estimated that in 1995 40,000 Americans will die from prostate cancer and 45,000 will die from colorectal cancer. The mortality rate for prostate cancer increased 23% from 1973 to 1992. The mortality rate for colorectal cancer decreased 17% over this same period.

AFRICAN-AMERICAN MALES AND CANCER

Mr. Stokes: In Testimony Before the Committee Last Year, Dr. Broder, Director of the NCI, at that time, told the committee that African American males have the highest rate of prostate cancer than any other segment of the world's population. To what extent has the number of cases been increasing?

Dr. Sondik: The incidence (number of new cases) rate of prostate cancer has increased 170 percent between 1973 and 1992. The increase was greater among white males than African American males. African American males, however, continue to have much higher rates (243 per 100,00) than white males (179 per 100,000). The number of men predicted to be diagnosed with prostate cancer reached an all-time high in 1995: 244,000.

PROSTATE CANCER RESEARCH

Mr. Stokes: In the report accompanying the appropriations bill last year, the committee included language encouraging the Institute to expand its commitment to the prostate research program and to place emphasis on research geared toward the development of effective early detection technologies and innovative treatments for the disease. Would you bring the committee up-to-date on activities in this area?

Dr. Sondik: The National Cancer Institute (NCI), as the lead Institute of the National Institutes of Health (NIH) responsible for prostate cancer research, supports and coordinates a multidisciplinary research agenda to address fundamental issues in cancer etiology, epidemiology, tumor biology, vaccine development, prevention, early detection and diagnosis, and treatment. To achieve the goals of eradication of death and suffering from prostate cancer, the NCI cooperates and collaborates with the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), the National Institute of Aging (NIA), the National Institute of Child Health and Human Development (NICHD), the National Institute of Environmental Health Sciences (NIEHS) and other sister agencies of government. For example, NCI contributes to NIDDK's Urology Research Centers Request (the O'Brien Research Centers Program) by providing support for prostate cancer investigation. NIEHS and the Environmental Protection Agency (EPA) are active collaborators in NCI's pivotal Agriculture Health Study, in which prostate cancer is a major focus. The Veterans Administration (VA) and the NCI Clinical Cooperative Groups collaborate in a pivotal clinical protocol, the Prostate Intervention versus Observation Trial (PIVOT), to determine the role of aggressive surgical intervention in the management and survival of men with early-stage prostate cancer. Moreover, the oncology communities of essentially every NCI Cancer Center are intensifying their research portfolios to address the important challenges of prostate cancer and to change the impact that prostate cancer presently has on the duration, productivity and quality of life for all men who are affected by this disease.

The recent development of innovative animal models of prostate cancer that bear resemblance to the human disease are crucially important to the study of prostate cancer biology, prevention and therapy. The unique transgenic mouse prostate reconstitution (MPR) model, developed by scientists at the Matsunaga-Conte Specialized Program of Research Excellence (SPORE) at Baylor University, and other novel xenograft models of human prostate cancer cell lines are providing fertile testing grounds that have been not been available up until now.

The tragically high mortality of prostate cancer in African-American males is an area of intense investigation. Indeed, the increase in prostate cancer mortality over the last 20 years in African American men is almost twice that of white Americans. Recent epidemiologic studies have demonstrated that the excess mortality of African-American men in the Southeastern United States relative to African-American men in other parts of the country may be linked to employment in farming. Studies comparing African-Americans and white Americans demonstrate that both groups have similar age-specific baseline serum levels of Prostate Specific Antigen (PSA) and similar familial risks. The large-scale

Agriculture Health Study, the Migrant Farm Workers Study, the Triana Study (in conjunction with the Tennessee Valley Authority) and the epidemiologic studies accompanying the landmark Prostate Cancer Prevention Trial (PCPT) will shed important light on these issues. In addition, the prostate cancer SPOREs are specifically examining the differential expressions of certain genes and serological biomarkers in the context of racial/ethnic differences. NCI has recently issued two Requests for Application (RFAs) for funding within the next 6-12 months -- "The Molecular Epidemiology of Prostate Cancer" (using the R01 mechanism) and "Prostate Cancer Programs within Cancer Centers" (using the new R21 mechanism) -- to stimulate innovative clinical investigations in this research area. In addition, NCI proposes to develop a new RFA, "Prediction of Prostate Cancer in African American Men," with a special focus on the identification of biomarkers and biological parameters as predictors of prostate cancer risk and tumor biology in this population,

The genetics of prostate cancer are unfolding as a result of basic research. The inheritance of prostate cancer bears notable similarities to the inheritance of breast cancer, and many groups of intramural and extramural investigators are rapidly closing in on potential "prostate cancer genes." Provocatively, some cases of familial prostate cancer may be linked to the "breast cancer-1" (BRCA-1) gene. A recent exciting finding from the Johns Hopkins Prostate SPORE is that a gene responsible for detoxifying potential carcinogens -- one of the so-called glutathione-S-transferase (GST) genes of the *pi* class (GSTP-1) -- is consistently altered in cancerous prostatic cells (but not in noncancerous cells) such that its expression is suppressed. This exciting discovery may serve as a sensitive and specific tool for early detection, risk identification and perhaps monitoring of the effects of a therapeutic or prevention intervention. The development of agents to reverse the GSTP-1 alterations could form the basis for a targeted chemoprevention strategy.

NCI-sponsored research is making long strides in understanding prostate cancer tumor biology. This effort, as well as the effort to elucidate the genetics of prostate cancer, continues to be enhanced by the NCI-supported Cooperative Network for Molecular Genetic and Cytogenetic Markers for Prostate Cancer, a network of six research groups. The dissection of critical components such as new blood vessel development (angiogenesis), mutations in the androgen receptors present on the prostate cancer cell surface, the interactive molecules responsible for intercellular communications and adhesion, and the proteins that comprise the critical structural scaffold within the nucleus (the nuclear matrix) is leading to novel ways to define the specific properties of the cell that confer malignant behavior and to discriminate nonmalignant from malignant cells. In addition, each of these components is a ripe target for therapy and for the prevention of critical transforming events, for instance metastasis (tumor dissemination).

Novel vaccine candidates that target prostate cancer are now beginning to enter the clinical testing arena at a rapid pace. Mutations in the ras oncogene and overexpression of the encoded Ras proteins are often found in prostate cancer, and NCI scientists are already beginning to test vaccine constructs that use these abnormal proteins and peptides (portions of the proteins) to generate immune responses. The PSA protein is a potentially fruitful immunological target: PSA peptides and a vaccine linking the gene for PSA with the highly immunogenic recominbinant vaccinia vector will enter clinical testing within the year. Scientists at the Johns Hopkins SPORE are embarking on a gene therapy-based vaccine that will be tested in an adjuvant setting in men with Stage C prostate cancer. These are the first generation of studies in what promises to be a hotly-pursued area over the next several years.

The landmark PCPT is testing the role of finasteride (Proscar), an inhibitor of the 5-alpha-reductase enzyme which converts testosterone into the active metabolite dihydrotestosterone (DHT) within the prostate, as a potential preventive agent for prostate cancer. This study, launched in October 1993, is being conducted through the Clinical Cooperative Groups, led by the Southwest Oncology Group (SWOG) with 223 participating institutions. The PCPT is accruing men over age 54 and with PSA less than 3 ug/l at a peak rate of about 2,000 men per month (average about 1,000 per month); more than 22,000 men have been enrolled and about 14,000 men are currently on study (the target is 18,000 men). To date, roughly 7.5 percent of the study population are minorities (4 percent African-American, 3.5 percent Hispanic). In addition to clinical outcome regarding finasteride-based prevention, the PCPT has established a serum and tissue bank for serially-obtained clinical samples that, in turn, will provide fundamental data regarding normal and malignant prostate biology, genetic and environmental/occupational epidemiology, screening/early detection (measuring the impact of finasteride on serum PSA levels), and any finasteride-induced changes in lipid metabolism. Since approximately 1 million men in the United States are taking finasteride for therapy of benign prostatic hypertrophy, the study will expand several facets of knowledge regarding this widely-used drug and, in this way, stands to serve diverse aspects of men's health.

Another large-scale trial underway is the Prostate, Lung, Colon and Ovary (PLCO) trial, a randomized trial to determine the value of routine screening for prostate, lung, colorectal and ovarian cancers by comparing intensive yearly screening for 4 years with routine medical care in 74,000 men and 74,000 women ages 60-74. Screening modalities for prostate cancer include digital rectal examination and serum PSA determination (and transrectal ultrasound if indicated). A 2-year pilot phase, accruing 14,000 participants, was completed in September 1994 and is being analyzed to determine any need for changes in study design, with special attention to whether or not certain screening modalities are already being performed routinely in the control group. The trial is being conducted at 10 institutions that are geographically distributed across the country.

The NIH and the NCI specifically have a direct responsibility to disseminate information relating to cancer research, diagnosis, prevention and treatment. A major prostate cancer educational campaign that includes mass media, launched by NCI's Office of Cancer Communications (OCC), focuses on early detection and treatment and targets older men, especially African Americans. NCI's International Cancer Information Center (ICIC) is responsible for information dissemination through scientific publications and databases. Its treatment database, Physician's Data Query (PDQ), provides data on state-of-the-art treatment for all major cancers; a geographically matrixed file of active research protocols enabling physicians to identify clinical trials appropriate for their cancer patients; an archival file of closed protocols; and a geographically organized directory of physicians and organizations providing cancer care. PDQ is unique in that the treatment information in PDQ is updated on a monthly basis by an editorial board of medical experts that continually scans cancer literature, synthesizes new data, and incorporates findings into disease and stage-specific treatment recommendations.

Clinical investigation of prostate cancer remains a critically high research priority, with dedicated involvement of intramural and extramural scientists, including NCI's Clinical Cooperative Groups. To this end, NCI's Cancer Drug Screen now has incorporated two human prostate cancer cell lines into its human tumor cell screening panel (with four additional lines under development), and has identified 150 compounds with degrees of selective activity against prostate cancer that are now undergoing targeted preclinical development, including testing in *in vivo* xenograft models. A key clinical study, mentioned above, is the VA/NCI Intergroup PIVOT study which compares aggressive surgical intervention with clinical observation in early stage prostate cancer. NCI plans to make this a High Priority Clinical Trial to speed recruitment to and completion of this study, which stands to define a state-of-the-art approach to early stage prostate cancer. A similar Cooperative Group study, beginning in 1995, is addressing the role of radiation therapy in the management of early stage prostate cancer, the Radiation Intervention versus Observation Trial (RIVOT). Indeed, the NCI Cooperative Groups are planning to implement 12 new Phase III trials of hormonal and cytotoxic agents in all stages of prostate cancer over the next 12-18 months. In addition, there are major clinical programs at the NIH Clinical Center and at NCI-sponsored institutions across the nation (especially but not exclusively the SPOREs and NCI Comprehensive Cancer Centers) aimed at testing new modalities: heavy particle and multi-dimensional radiation therapies, anti-angiogenesis strategies, inhibition of intracellular signaling pathways (both tyrosine kinase and Ras-based including isoprenylation), enhancement of programmed cell death, differentiation therapies (e.g. retinoids), and monoclonal antibody-based strategies (e.g. immunotoxins). This broad and rapidly expanding portfolio of clinical exploration is the direct outgrowth of the pivotal inroads now being carved into our understanding of cell and tissue biology on its most basic developmental levels and as it applies to the prostate.

In sum, this response provides a brief synopsis of NIH's cross-cutting basic and clinical investigations targeting prostate cancer research. There is a steep learning curve that, in turn, is generating excitement and progress in each area of investigation. And clearly, there is also a great distance to go before we accomplish the goal of disease eradication for the large numbers of men who stand to benefit from these efforts.

PROSTATE CANCER TREATMENT

Mr. Stokes: As there appears to be no consensus on the appropriate treatment for prostate cancer, to what extent would a joint NIH-CDC consensus conference on this disease and the development of a national plan be useful in helping to direct and focus basic, applied, clinical, and epidemiological research?

Dr. Sondik: At the present time, there is no consensus regarding many aspects of the management of prostate cancer, from screening and early detection to treatment at the various stages of disease and the possibility of prevention. In June 1987, the National Cancer Institute (NCI) held a Consensus Development Conference on the "Management of Clinically Localized Prostate Cancer." The conclusions reached at that time, and published in a 1988 Journal of the National Cancer Institute Monograph (Monograph #7), were that surgery (radical prostatectomy), radiation therapy and conservative management (observation) could be used to manage early-stage prostate cancer, but the relative merits of each alone or in combination were unknown. Along these lines, the American Urological Association (AUA) recently commissioned a literature review of the scientific data available on the therapy of early stage prostate cancer. The review panel included several NCI-supported scientists. This comprehensive review again failed to disclose a clear answer regarding the appropriate roles of surgery, radiation and/or clinical observation -- a conclusion that is not different from NCI Consensus Development Conference in June 1987 -- and supported the need for NCI's large-scale, randomized clinical trials (PIVOT and RIVOT, discussed below) to define the roles of each modality in the optimal management of early-stage prostate cancer.

To this end, the National Cancer Institute (NCI) is conducting three large-scale, randomized, controlled clinical trials that will shed great light on the optimal management of prostate cancer: 1) PIVOT (Prostate Intervention versus Observation Trial), a collaborative effort between the Veterans's Administration and the NCI Clinical Cooperative Groups Intergroup to determine the role of aggressive surgical intervention (radical prostatectomy) vs. observation and conservative management in early-stage (clinically localized) prostate cancer in 2,000 men; 2) PLCO (Prostate, Lung, Colon and Ovary) trial to determine the impact of routine PSA screening on early detection and survival of prostate cancer (and will also evaluate appropriate screening for colon and lung cancers) in 74,000 men ages 60-74; and 3) PCPT (Prostate Cancer Prevention Trial), evaluating the potential for the 5-alpha-reductase inhibitor finasteride (Proscar) to prevent prostate cancer in 18,000 men over age 54. A new large-scale, randomized trial being conducted by the NCI Intergroup beginning in 1995 -- RIVOT (Radiation Intervention versus Observation Trial) -- is similar in design to the PIVOT trial and will evaluate the role of early radiation vs. observation and conservative management in 2,000 men with early-stage disease. The results of these trials, as they become available individually and collectively, will form the basis for a Consensus Development Conference at a time when such a conference can be most informative.

There is an ongoing legitimate controversy regarding the efficacy of prostate cancer screening with the modalities presently at hand. Since 1988, there have been at least a dozen groups of experts from the United States, Canada and Europe who have scrutinized the value of seum PSA levels as a potential tool for the screening and early detection of asymptomatic, subclinical prostate cancer. While two of these groups felt that PSA-based screening should be conducted as part of standard medical practice, the other 10 groups, following extensive review of the available scientific data, concluded that the issue of PSA screening required an in-depth, well-controlled, large-scale clinical trial. Based on this controversy, NCI, with the expert advice from scientists at NIDDK, has developed and implemented the PLCO trial and the laboratory correlative studies within the framework of the PCPT. Further, in November 1993, the AUA in conjunction with NCI, the Centers for Disease Control and Prevention (CDCP) and the American Cancer Society (ACS) held a conference to address the current state of knowledge regarding prostate cancer screening. As a result of this conference, the AUA has endorsed the need for NCI's PLCO trial in order to place PSA-based screening in its proper context with regard to the overall management of prostate cancer, particularly in elderly men.

With regard to a national plan for prostate cancer research, the NIH supports a broad-based and comprehensive portfolio of intramural and extramural investigations that cover all research disciplines. The prostate cancer research agenda is informed by ongoing collaborations among NCI and the categorical NIH institutes, in particular NIDDK, National Institute of Environmental Health Sciences (NIEHS) and National Center of Human Genome Research (NCHGR), as well as close interactions with the AUA, ACS and CDC. The Agriculture Health Study -- the nation's largest-ever epidemiologic study of 100,000 farmers and their families -- is a collaboration effort among the NCI, NIEHS and the Environmental Protection Agency (EPA) to identify and assess factors that may relate to the detected excesses of certain cancers, including prostate cancer, among farmers. The demographic characteristics and identification of possible risk factors for prostate cancer are one major focus of this study. NCI contributes to NIDDK's Urology Research Centers Request (the O'Brien Research

Centers Program) by providing support for prostate cancer investigation. NCI and NIDDK are jointly sponsoring an upcoming Working Session on Prostate Cancer Prevention. Further, NIDDK scientists serve on NCI's advisory board for the development, implementation and evaluation of both the PLCO and PCPT trials. Interagency collaborations are also exemplified by the joint development of workshops and conferences such as: 1) 1993 Workshops on the Early Detection of Prostate Cancer -- one co-sponsored by NCI, CDC, AHCPR and the Navy Bureau of Medicine and Surgery and one co-sponsored by NCI, AUA and ACS; 2) 1993 Conference on Vasectomy and Prostate Cancer (NCI, NIDDK, NICHD); 3) 1994 Conference on Metal Ions in Biology and Medicine (NCI, Food and Drug Administration); and 4) Workshop on Dietary Phytoestrogens (NCI, NIEHS). The workshops and conferences define and evaluate the state of knowledge (and lack thereof) regarding the specific subject area, serve as cornerstones for identifying existing and emerging scientific opportunities, and form the basis for the development of Program Announcements and Requests for Applications for innovative research addressing such areas of scientific opportunity. The NCI also benefits from the input and active involvement of the advocacy group "Us Too" in the PCPT; members of "Us Too" are helping to recruit brothers of prostate cancer patients, as members of a potentially high risk subgroup, for possible entry into the PCPT.

PROSTATE CANCER FUNDING

Mr. Stokes: How much is included in the FY 1996 budget request for prostate cancer and how does this compare with the funding level for FY 1995 and FY 1994?

Dr. Sondik: The NCI prostate cancer funding estimate in 1996 is $61 million, an increase over the 1995 estimate of $59 million and the 1994 actual funding of $56 million.

EVALUATION OF THE NATIONAL CANCER PROGRAM

Mr. Stokes: The National Cancer Advisory Board's Subcommittee recently completed its evaluation of the National Cancer Program. Its report entitled *Cancer at a Crossroads: A Report to Congress for the Nation* is quite comprehensive and revealing. The document emphasizes the need for the Institute to strengthen its translational research effort. What is the appropriate program balance and mix for the Institute? To what extent is this being done, and what is the Institute's assessment of the report? How are the report's findings and recommendations being used by the Institute?

Dr. Sondik: The National Cancer Institute supports a comprehensive and coordinated cancer research program that includes basic research, research to develop better early detection and diagnostic technology, and research on prevention, treatment, rehabilitation, and community outreach strategies. NCI recognizes the importance of translational research to move basic research advances into applications that will have a direct impact on cancer incidence and mortality. Two important NCI programs, the Cancer Centers Program and Specialized Programs of Research Excellence (SPOREs) explore innovative approaches to cancer through interactive, cross-disciplinary efforts. Through these programs, discoveries from basic research can be applied to patients and, conversely, clinical research findings can stimulate laboratory studies that may lead to new interventions.

NCI welcomes the recommendations contained in the report of the Subcommittee to Evaluate the National Cancer Program (SENCAP) to help the Institute meet the formidable challenges for reducing the burden of cancer. NCI, in consultation with the full National Cancer Advisory Board (NCAB), will consider these recommendations in setting priorities for future cancer research directions. Some activities are underway.

- SENCAP recommended a detailed evaluation of NCI's intramural program that would take into account the recent evaluation of the NIH Intramural Research Program requested by the House of Representatives. An ad hoc external working group chaired by NCAB members Dr. J. Michael Bishop and Dr. Paul Calabresi is conducting a review and an evaluation of the NCI's intramural program. The findings of this group are expected to be presented in May 1995, and will be considered in the context of the SENCAP recommendations.

- The NCAB has assigned each recommendation to one of its subcommittees for review. The subcommittees will identify those recommendations which are most important, most likely to be successfully implemented, or for which there are adequate resources. The Board will advise NCI about priorities and implementation when the review is complete.

- SENCAP recommended an inventory and analysis of cancer research related activities across Federal agencies. NCI recently received NIH evaluation set-aside funds to support a pilot of this activity. The project is scheduled to begin in the late spring of 1995.

DESIGNER THERAPIES

Mr. Stokes: Are we making much progress in the development of designer therapies, that is tumor-specific customized therapies and specially constructed antibodies that can carry a therapy right to the cancer cell?

Dr. Sondik: All cancer therapies including cytotoxic drugs such as taxol and cisplatin are based on differential effects on tumor versus normal tissue. These therapies to date have had limited, but important, efficacy in a number of tumor types. The impressive advances in the understanding of cancer cell biology, nonetheless, lead to the conclusion that there are most likely few cancer-specific targets. However, several relative differences between cancer and normal cells can be exploited to increase the therapeutic ratio against tumors with acceptable levels of toxicity.

A number of antibody-toxin constructs or radiolabelled antibodies (to deliver radiation at the site of tumor), as well as "naked" or unlabelled antibodies, are in clinical trials. Although there are no known targets that are specifically restricted to tumor tissue, the targets of these antibodies are expressed preferentially or found more generally on tumor cells. For example, the targets include the IL-2 receptor (for T-cell lymphomas/leukemia), CD19, CD20, and CD22 (for B-cell lymphomas and leukemias), TAG-72 (colon, breast, ovarian and prostate cancer), her-2-neu (a growth factor receptor over-expressed on breast and ovarian cancers), the EGF receptor (another growth factor receptor over expressed on numerous malignancies including lung cancers), and gangliosides (expressed on melanomas and some neural crest tumors). Clinical responses have been observed in many of these trials but it is still too early to determine the efficacy of these agents.

Vaccines induce cell-mediated and antibody responses against tumor antigens. The lymphocytes that mediate cell-mediated immune responses actually recognize portions of intracellular proteins. Recently, investigators have shown that mutated proteins that are found only in tumor cells can be recognized by the immune system. Therefore, it is now possible to generate a vaccine from a tumor that will raise an immune response specific to the tumor. An example is a vaccine against the mutated p53 protein which is prepared individually from each patient. Another example is the vaccine prepared against the mutated ras oncogenes (pancreas and lung cancers, among others). Clinical results with these vaccines are not yet available. Several other vaccines, against melanoma, prostate cancer, colon cancer, and several other tumors, that recognize normal proteins that are expressed almost exclusively in tumor tissue, are being developed. These include the MART-1 and GP100 antigens in melanoma, prostate-specific antigen for prostate cancer, and CEA for colon cancer.

A third relatively tumor-specific treatment involves strategies that attack tumor vasculature (blood vessels). Tumors cannot survive or grow without the formation and maintenance of their blood supply. We know that the formation of tumor vessels occurs in response to specific growth factors. The effect of these growth factors can be blocked by some naturally occurring agents, as was shown in animal models for the recently identified compound called angiostatin. The receptors for these growth factors are also relatively restricted to tumor vessels, so that the growth factor can be given linked to a toxin that will kill the cells. Recently, the forming tumor blood vessels (in contrast to normal vessels) were shown to express certain adhesion molecules (integrins) that can be targeted with antibodies or antibody-toxin conjugates. Preliminary preclinical results show that attacking these integrin molecules can cause the tumor blood vessels to dissolve, and tumors to shrink. Finally , a compound isolated from bacteria (CM-101) that binds relatively specifically to tumor blood vessels, and induces an inflammatory response that results in their destruction, has recently entered clinical trials.

Among the most exciting basic science discoveries in the past 2 years is the demonstration that an enzyme, telomerase, responsible for replicating the ends of chromosomes, is found almost exclusively in immortalized (continually dividing) cancer cells. Normal cells do not express this enzyme, so that as cells go through normal divisions, the ends of the chromosomes become progressively shorter, until the damage to DNA induces senescence and cell death. Cancer cells turn on this enzyme, which allows them to grow and divide indefinitely, i.e., they become immortal. There is substantial promise in attacking or inhibiting this enzyme as a means to shorten the life-span of cancer cells.

Other basic science advances suggest the potential for relatively specific tumor delivery and expression of genes that will kill the tumor cell or prevent it from growing and dividing. Progress has been made, for example, in redirecting the target for infection by certain retroviruses, suggesting the possibility that these viruses could be used to deliver genes to specific cells. Progress has also been made in achieving relatively specific expression of genes by adding promoters (switches for gene expression) that would 'turn on' only in the cancer cell. These approaches to treat cancer, however, are at least several years away.

Finally, a number of agents are being developed that prevent the relatively tumor-specific processes of invasion and metastases, or that induce tumor cell differentiation. These agents include CAI, the retinoids, peryllil alcohol, and phenylacetate, among others. We anticipate that the agent all-trans-retinoic acid (ATRA) will soon be approved by FDA for the treatment of patients with acute promyelocytic leukemia (APL). The ability of ATRA to induce differentiation in vivo of APL cells has led to a marked improvement in the expected outcome for these patients.

DIET AND CANCER

Mr. Stokes: According to your opening statement, four in ten of us will have a personal experience with cancer during our lives, and one in five of us will die of cancer. As researchers continue to unravel the relationship between cancer and nutrition, are we disseminating the information expeditiously? What percentages of cancers are related to diet?

Dr. Sondik: The National Cancer Institute actively supports cancer information dissemination activities. NCI works to ensure that the public and health professionals are afforded easy access to up-to-date information regarding cancer prevention and treatment as it relates to diet and cancer.

Early nutrition research focused on identifying essential nutrients and helping individuals or populations avoid diseases associated with nutritional deficiencies. The benefits included improved growth and development, particularly for young children. More recently, as the average age of the population has increased and more emphasis has been placed on the public health impact of chronic diseases, a shift in research priorities has taken place. There has been an increased focus on diseases at all ages, including the elderly, and greater awareness of the need to expand the existing nutritional research paradigm from simply avoidance of deficiencies to a new focus on optimizing nutritional intake. Over the past decade, diet and nutrition research at the NCI has grown in size and scope. Today, NCI has an array of activities -- both intramural and extramural -- that address many of the fundamental issues in diet and its relationship to cancer. The overall goal is to provide more definitive data for developing quantitative dietary guidance and acceptable food choices that have the potential to substantially reduce the risk of cancer in the general population. The recent advances in scientific technology enable the coupling of basic and clinical aspects of nutrition research.

The considerable progress of the past 10 years strongly suggests that our understanding of cancer can be expanded many-fold if the new tools of the cancer biologists are coupled sufficiently with clinical and epidemiological nutrition research. The expansion of focus to include all aspects of research -- from the study of the most fundamental biological processes to dietary intervention trials, epidemiology, surveillance, and applications research -- is a paradigm for the future. Until very recently, the explosion of ideas and technology for monitoring cancer pathways has not focused on mechanisms that are activated or mediated by nutrition. NCI will bring its resources to bear so as to more fully understand how dietary components provide a defense against cancer or stimulate its development. With rare exception, the development of chronic disease is a multifactorial process in which diet and nutrition may play a key role. In years to come, nutrition research will be of importance not only to cancer prevention but to the control of many other diseases.

Among the highest priorities for future NCI research is the development of better techniques to identify high-risk populations to target for intervention strategies, including dietary and nutritional interventions, and the advancement of more promising agents to test in these high-risk populations. Intervention strategies will benefit from the development of new assays and an improved understanding of the relationship between cellular and biochemical parameters and tumor development. This work will provide the rationale for moving from promising preclinical and epidemiologic data to clinical trials. To date, nutritional intervention studies have been hampered by a relative lack of intermediate endpoints and reliable markers of dietary intake to monitor the impact of dietary changes on the carcinogenic pathway. The availability of such intermediate molecular endpoints or premalignant lesions (for example, colon polyps) that correlate with earlier stages of carcinogenesis will reduce the time, cost, and number of patients required to complete an intervention trial. In addition, the development of molecular biomarkers using genetic and biochemical technologies will add a new dimension to the identification of high-risk populations for intervention clinical trials.

NCI's plan for an expanded agenda in nutrition research is built upon the existing program but further developed to create a new research model -- applying the latest epidemiological, physiological, behavioral, molecular, cellular, and genetic technologies to nutrition and cancer research while facilitating the evaluation of research results and their application in the public health environment. The dissemination of information relevant to this area is vital and of extreme interest to the NCI. As an example, since its inception in 1991, the "5 A Day for Better Health" program has proven to be one of the nation's most widely recognized health promotion programs. The program's strength is the combined effort of the National Cancer Institute and the Produce for Better Health Foundation (PBH), a network of food companies and supermarkets. The goal of this program is to make Americans aware of how eating fruits and vegetables can improve their health and reduce the risk of cancer. This program not only encourages eating five or more servings of fruits and vegetables every day, but also offers easy practical ways to include them in the diet.

NCI supports the 5 A Day program by conducting a media campaign targeted to consumers and provides consumer education brochures to the public and to health professionals. NCI has awarded nine 4-year research grants to state health agencies, universities, and cancer centers to evaluate the effect of 5 A Day activities in schools, workplaces, and other community settings. State health agencies also coordinate the 5 A Day activities of participating health organizations and are working cooperatively with industry participants to promote the program's messages in the marketplace to consumers.

PBH serves as the central coordinator for members of industry involved in spreading the 5 A Day messages. PBH membership embraces virtually all corners of the fruit and vegetable industry, including fresh, frozen, dried, and canned. Members include retailers, growers, shippers, packaging manufacturers, and marketing organizations.

More than 30,000 retail food stores nationwide annually promote 5-A-Day in stores, through materials such as posters, brochures, recipe cards, and tip cards.

The Cancer Information Service (CIS), known to the public as 1-800-4-CANCER, is staffed by information specialists equipped to respond to public inquiries regarding cancer including those that are diet related. Over one-half of the callers receive a publication or other written material through the CIS's Publications Ordering Service (POS). The CIS consists of a nationwide network of 19 regional offices, 18 of which receive direct NCI funding. In addition to providing direct response to the public, the field offices support NCI's major outreach activities and conduct cancer education programs including nutrition education programs to meet specific local and regional needs.

NCI provides nutrition education brochures through the POS addressing the NCI's Dietary Guidelines including the need to decrease fat and increase fiber for a variety of healthy populations to help reduce cancer risk. Selected nutrition information for consumers is available on the Internet through Cancer Net. NCI also provides nutrition education materials for cancer patients through the Cancer Information Service's POS.

It has been estimated that 35 percent of cancer deaths may be related to dietary components, with the possible range of effect being 10 percent to 70 percent.

These estimates cannot be considered definitive because research to test the effectiveness of dietary interventions to reduce cancer incidence and mortality for particular sites is only now under way. Nevertheless, even the most conservative estimate represents a potentially significant impact on cancer mortality. Meanwhile, a consensus is growing that certain changes in diet are prudent at this time because they may be important in reducing cancer incidence.

DIET AND CANCER IN AFRICAN-AMERICAN FEMALES

Mr. Stokes. What is the status of the Institute's initiative to study the impact of diet on cancer in African American females? How much is included in the FY 1996 budget request for this initiative, and how does it compare to FY 1995 and 1994?

Dr. Sondik. This initiative encourages investigator-initiated grant applications for studies to develop and evaluate the effectiveness of culturally sensitive intervention strategies to assist African Americans in adopting eating patterns consistent with the NCI Dietary Guidelines.

Specifically, the research focuses on 4 areas: (1) identification of barriers and motivators of dietary change among African Americans; (2) development of culturally sensitive intervention strategies to increase knowledge and promote attitude and dietary behavior change among African Americans; (3) evaluation of the effectiveness of culturally sensitive intervention strategies in achieving and maintaining eating habits consistent with the dietary guidelines, and (4) evaluation of the impact of dietary changes on biochemical and anthropometric parameters.

Applications are solicited by an ongoing Program Announcement, first issued in February, 1994. Five applications were received for the June 1, 1994 NIH grant application submission date and 5 applications were received for the October, 1994 submission date. The 10 applications have been reviewed for scientific merit through the NIH peer-review process. All applications were beyond the fundable payline. Thus, to date, no grant applications for this initiative have been funded. The investigators plan to revise and resubmit their applications.

CANCER AND THE ENVIRONMENT

Mr. Stokes: What percentage of known cancers are caused by environmental factors, and which of these cancers are more prevalent in the United States?

Dr. Sondik: It has been widely reported that the bulk of all cancer in the United States is related to environmental factors, particularly those involving lifestyle practices. These estimates are derived not from a detailed understanding of cancer causes but rather from the substantial international variation in cancer incidence. The role of environmental factors is reflected also by the variation in cancer rates over time, although some fluctuations can be anticipated by changing medical and reporting practices. Most dramatic has been the long-term increase in lung cancer related to smoking in the United States, along with a decline in stomach cancer for reasons that are not entirely clear. In recent years, upward trends in incidence have been reported for several tumors, including melanoma, non-Hodgkin's lymphoma, multiple myeloma, and cancers of the breast, prostate, and testis. Also deserving of further study are the racial and ethnic disparities of cancer in the United States, including the higher incidence among blacks for multiple myeloma and cancers of the esophagus, stomach, pancreas, prostate, lung, and cervix.

By far the principal carcinogenic hazard in Western countries is tobacco smoking, which has been firmly linked not only to lung cancer but also to cancers of the larynx, mouth, pharynx, esophagus, bladder, and pancreas. Recent evidence suggests that smokers are also prone to cancers of the kidney, uterine cervix, nasal passages, and perhaps also to stomach cancer and leukemia. In the United States, it appears that smoking, especially of cigarettes, accounts for about 40% of all cancer deaths among men and about 20% among women. However, in recent years the rates for lung cancer have been rising more sharply in women than in men, reflecting the growing popularity of cigarettes among women in the past three decades. Epidemics of smoking-related cancers are also starting to emerge in developing countries around the world. In addition, passive smoking has been hotly debated as a risk factor for lung cancer, and evidence for a causal relationship has accumulated. A review of the available evidence suggests that non-smoking women married to smokers have experienced an excess risk of the order of 30%, with risks rising to about 70% among the most heavily exposed nonsmokers. Smokeless tobacco is also of concern since oral cancer has been linked with snuff dipping, a common practice in rural southern parts of the United States. Under suspicion are the high levels of tobacco-specific nitrosamines that have been detected in snuff and in the saliva of snuff users.

Overall, these findings have prompted recent public health and legislative measures in the United States aimed at discouraging the use of smokeless tobacco, especially among young people.

Consumption of alcoholic beverages has been shown to potentiate the effects of tobacco smoke on cancers of the mouth, pharynx, esophagus, and larynx. In a large-scale study of oral cancer, it was found that the risks increased with intake of alcohol even among nonsmokers, but in combination with smoking, the risks multiplied to 35-fold among heavy consumers of both products. In the United States, the risks for esophageal cancer are higher among blacks than whites, especially black men in urban areas, but the highest rates on the cancer maps are seen among black residents in the rural eastern part of South Carolina. In this area a case-control study revealed sharply elevated risks from drinking alcohol, especially moonshine or home-brewed whiskey, samples of which are being examined for contaminants that might be carcinogenic. Alcohol intake has been linked also to liver cancer, and if the associations described in some recent studies of breast and colorectal cancers are confirmed, the amount of cancer related to alcohol would surpass the 3% previously estimated.

International correlations and migrant studies have suggested that certain features of the Western diet contribute to a large but uncertain proportion of all cancers. Various hypotheses about causative and protective factors are under study, but the specific dietary components are elusive and the mechanisms of action appear complex. The roles of dietary fat, calories, meat intake, obesity, and body size remain to be sorted out in cancers of the large bowel, breast, and reproductive sites. A remarkably consistent finding is the protective effect of fresh fruits and vegetables in cancer of the lung and various other sites along the digestive tract. The effect has been attributed by some workers to carotenoids, especially with regard to lung cancer. However, other studies have suggested that vitamins C and E and allium vegetables may protect against stomach cancer, whereas intake of fiber and cruciferous vegetables may lower the risk of colon cancer. In view of the limitations of nutritional methods in epidemiology, further progress is likely to depend on innovative analytical studies employing biochemical assays, as well as intervention studies involving dietary supplements and modifications.

Along with tobacco smoking, more is known about the carcinogenic effects of ionizing radiation than almost any other human carcinogen. However, it is difficult to measure directly the effects of low doses of ionizing radiation, although extrapolations are possible by studying populations that have been exposed to high and moderate doses for medical, occupational, or military reasons. It has been estimated that 1 to 2% of cancer deaths may be attributed to background radiation. However, the upper limit may increase if risks of lung cancer associated with indoor levels of radon are consistent with recent estimates that have been derived from the experience of underground miners exposed to relatively high doses of a-radiation.

Occupational exposures are usually reported to account for about 5% of all cancer deaths, but the percentage is higher in certain regions and for certain tumors, such as lung and bladder cancers; and it may change as new hazards are recognized or as protective measures are instituted. Despite this uncertainty, it is clear that no other approach has identified so many human carcinogens as the study of occupational groups. The exposures also have broader implications, since most agents are not confined to the workplace but ultimately become part of the general environment to which large segments of the population may be exposed. Asbestos represents the main occupational carcinogen in many countries, due mainly to its induction of lung cancer rather than mesothelioma. Its impact can be seen on the United States maps for lung cancer, which have shown exceptionally high rates along the southeast Atlantic coast, due to asbestos exposures in shipyards, many of which operated during World War 11 and then were closed. As in other studies of asbestos-exposed groups, a synergistic interaction was found between shipyard work and smoking in the development of lung cancer. The mapping of bladder cancer also seems influenced by occupational exposures, with rates in men being particularly high in sections of the northeast and urban areas around the Great Lakes. In some areas, associations were found with chemical and petrochemical exposures, and a previously unsuspected risk was detected among truck drivers and other groups exposed to motor exhausts. In addition, a recent cluster of non-Hodgkin's lymphoma has emerged in Kansas, prompting a case-control study that revealed an excess risk among farmers exposed to phenoxyacetic acid herbicides.

Pollutants in the urban air have long been suspected in the etiology of lung cancer, with fossil fuel combustion products, especially polycyclic hydrocarbons, being a special concern. However, it has been difficult to obtain good estimates of exposure and to disentangle the effects of smoking and occupational hazards. Recently implicated is inorganic arsenic since increased rates of lung cancer have been found in the neighborhood of arsenic-emitting smelters that cannot be explained by smoking or occupational exposures. There is much current interest in the role of indoor air pollution by radon gas, tobacco smoke, and other exposures. Special opportunities for study exist in China where the high rates of lung cancer among non-smoking women have been related to cooking oil vapors generated by high-temperature wok cooking and to effluents from coal heating stoves. Also under study are contaminants in drinking water, especially since an excess risk of bladder cancer was associated with long-term intake of surface water containing halogenated organic compounds produced during chlorination. Studies are under way to see if this risk can be confirmed and whether it may extend to other cancers. Only about 2% of cancer deaths have been attributed by Doll and Peto (The Causes of Cancer, Journal of the National Cancer Institute, vol. 66, p. 1191, 1981) to environmental pollution, but this estimate is based on limited data and may be modified upward by the results of ongoing research.

IMMUNOLOGY RESEARCH AND TUBERCULOSIS

Mr. Stokes: The Institute has done extensive research in immunology and strengthening the immune system. To what extent is that knowledge being applied to the re-emergence of tuberculosis? How much is included in the FY 1996 budget request for this initiative. And how does it compare to FY 1995 and 1994?

Dr. Sondik: Immunology is a fast-moving field in which discoveries made in one disease provide important new clues in others. Included in the 1996 NCI budget request is $183 million for immunology research across all areas. The estimated budget for immunology research for FY 1995 is $180 million and the actual expenditures for FY 1994 was $177 million. Immunology research supported by NCI has contributed to advances in infectious diseases and autoimmunity, as well as cancer. Many of the best immunologists in the country spend time working on all of these problems because they recognize that each provides a unique window on the functioning of the immune system. While NCI does not conduct research directly related to tuberculosis, there are several parallels between the immune response in cancer and tuberculosis that make research on one particularly applicable to the other. Both tumor cells and tubercle bacilli are initially recognized by the immune system, but the immune response fails to completely eradicate the challenge, and eventually comes to ignore it. In both cases, the cellular arm of the immune system appears to be the key to a more effective immune response. Both cancer and tuberculosis lead to a significant loss of immune function in the patient. Specific advances made in cancer immunology that are relevant to tuberculosis research include improvements in understanding how T lymphocytes recognize malignant cells, new strategies for vaccine development, and a better appreciation of the roles and clinical potential of cytokine therapy.

AIDS RESEARCH

Mr. Stokes: What is the most significant AIDS research that is underway at your institution?

Dr. Sondik: The AIDS pandemic continues to impose tremendous death and suffering on a global scale. Over the 13 years since AIDS was recognized as a distinctive clinical entity and in the decade since the retrovirus known as HIV was discovered as the causative agent, the National Cancer Institute (NCI) has maintained an unwavering commitment to all disciplines of basic and clinical AIDS research. This commitment to AIDS research is a direct outgrowth of scientific areas where intramural NCI scientists have made pioneering contributions: genetic immunodeficiency syndromes linked to cancer predispositions (ataxia-telangiectasia and Wiskott-Aldrich syndrome as examples) and viral cancers, in particular those relating to retroviral infections. These historical areas of research expertise within the intramural program have served as foundation stones for the clinical observations and basic interests of NCI scientists in AIDS research. NCI epidemiologists were involved in the initial demographic and viral studies of the AIDS epidemic and NCI clinical investigators were among the first on the NIH campus to diagnose and care for a patient with AIDS in 1981. NCI investigators reprogrammed their laboratory efforts to study the AIDS epidemic in many directions, including viral genetics and critical growth factors (cytokines) that affect immune balance.

HIV RESEARCH:

To date, NCI's research has made some impact on the natural history of progressive HIV infection. NCI investigators developed and brought to the clinic the complement of anti-HIV drugs currently approved by the Food and Drug Administration (FDA) for treatment of HIV infection. The initial clinical trials were designed and conducted by NCI. The Pediatrics Branch of the Clinical Oncology Program of NCI has made pioneering contributions to drug development as it applies to infants and children in particular and to understanding the unique pathophysiology (and designing treatment) of central nervous system involvement by HIV. The Pediatrics Branch pioneered the developmental clinical trials of ddI that led FDA in October 1991 to approve ddI simultaneously for AZT-refractory adults and children, an unprecedented event.

Still, new challenges are confounding the vector of progress toward enhancing the duration and quality of survival of the HIV-infected individual. Some of these emerging areas of focus include the development of resistance to antiretroviral agents, the abrogation of maternal-fetal HIV transmission, the emergence of multidrug resistant tuberculosis as a major opportunistic pathogen and the complex issues surrounding tumorigenesis in the state of profound and protracted immunosuppression. As such areas of scientific opportunity unfold, NCI continues to expand the boundaries of its HIV research portfolio to encompass these important barriers to the ultimate goal, namely the eventual eradication of progressive HIV infection, its sequelae and AIDS.

NCI-supported investigators, intramural and extramural, are making important inroads into diverse aspects of the etiology and pathogenesis of HIV disease. The immunopathogenesis of progressive HIV infection is a complex interaction between host and virus that is mediated to a large degree by numerous cytokines that modulate the activities of diverse immune-active cell subsets. In this light, the finding by NCI scientists that the balance of the two subsets of helper T cells is distorted as HIV disease progresses to full-blown AIDS has important implications for both the design and the monitoring of therapeutic and preventive interventions, including vaccine development. Further, HIV interacts with various host genes to subvert host cell machinery, disrupt normal cellular metabolism and thereby dysregulate the cellular mechanisms that maintain the normal balance of cell proliferation, differentiation, survival and death. For instance, the HIV nef gene may play a central role in HIV pathogenicity by interfering with normal host signaling pathways and thereby maintaining a high viral load. Since the presence of latent (non-replicative), "sequestered" HIV hampers the ability to eradicate viral infection through virocidal drugs or immune-based strategies, the dissection of factors involved in shifting the balance between latency and active replication could have important therapeutic implications. The development of novel animal models -- the pig-tailed macaque, the bovine immunodeficiency virus (BIV)-infected rabbit model and the severe combined immunodeficiency (SCID) mouse model -- is crucial to the basic understanding of HIV infection. Each of these selected components of NCI's basic investigations will have fundamental implications regarding vaccine development, the identification and exploitation of new molecular targets for antiretroviral and antitumor therapies, and the prevention of HIV-related malignancies.

AIDS VACCINE DEVELOPMENT:

NCI scientists continue to support the AIDS vaccine effort, maintaining a focus on genetically engineered vaccines. Synthetic peptide vaccines, using segments of the HIV envelope and reverse transcriptase enzyme proteins that are recognized by multiple histocompatibility types (cluster peptides) to elicit both cytotoxic T cell and neutralizing antibody responses in a large and heterogenous population, are about to enter the domain of clinical testing at the NIH Clinical Center. Non-infectious viral particles with heightened immunogenicity and novel recombinant vaccines using recombinant or live vectors (e.g. vaccinia, avipox and influenza) and recombinantly-produced HIV protein subunits are being tested in animal models for their abilities to protect against both mucosal and intravenous virus challenge.

NCI continues its intensive efforts in anti-HIV drug development, ranging from new drug discovery and preclinical development to clinical trials of promising agents in adults and children. NCI's high-capacity AIDS Drug Screen has a special focus on the identification of natural products with unique structures and mechanisms of action. Diverse chemically and mechanistically distinctive natural products have been discovered in the AIDS Drug Screen and are in various stages of preclinical and clinical development -- michellamine B (entering Phase I clinical trial) conocurvone, costatolide, calanolide A and prostatrin, as examples. The unique hollow fiber assay, adapted from NCI's Cancer Drug Screen, is capable of measuring evidence of viral replication (plasma p24, reverse transcriptase in fibers) and detecting differential activity of antiretroviral compounds, thus providing a novel *in vivo* system for antiretroviral drug sensitivity testing. The translation of molecular virology into antiretroviral therapies, such as those targeting the reverse transcriptase enzyme (congeners of AZT, ddI, ddC) or the HIV protease, remains a high priority. Indeed, NCI's supercomputer plays a major role in defining the structures of these targets and providing the groundwork for rational drug design aimed at these viral enzymes. NCI's AIDS Antiviral Drug Screen has recently uncovered an active compound with an unprecedented mechanism of action, namely the disruption of the highly conserved zinc finger regions of the HIV nucleocapsid protein, p7. HIV integrase (encoded by the HIV pol gene) provides yet another novel target for inhibition in both HIV infection and in HIV-related lymphomas. In addition to new agents targeting specific molecular virologic mechanisms, the design and implementation of innovative modalities including immunopotentiating growth factors, applications of biochemical pharmacology and complementary combinations of antiretroviral agents aimed at abrogating drug resistance are pivotal investigative priorities. Precedent-setting clinical trials to test such new concepts and modalities are core components of the NCI AIDS clinical efforts of Medicine Branch and Pediatrics Branch of NCI's Clinical Oncology Program. Genetic engineering for the purposes of immune reconstitution and development of antisense constructs to block transcription of viral genes are being developed.

RESEARCH OF AIDS-RELATED MALIGNANCIES:

NCI is uniquely dedicated to the fostering of basic and clinical investigation of AIDS-related malignancies, notably AIDS-Kaposi's sarcoma (KS), HPV-associated anogenital cancers, and AIDS-related lymphomas. NCI investigators have made pivotal contributions to the discovery and dissection of the formative roles that diverse host cytokines (especially those that induce new blood vessel formation, or angiogenesis) and the interactions of host cytokines with viral gene products (namely the HIV Tat protein) play in the etiology and pathophysiology of AIDS-KS. Further, intramural epidemiologists and clinical investigators made the landmark observation that AIDS lymphomas arise following protracted AZT therapy as a consequence of prolonged survival in the chronically immunosuppressed state. Indeed, it was following the recognition of this ironic and tragic consequence that the extramural oncology community became increasingly involved in basic and clinical investigation of AIDS-related malignancies. To enhance and support the involvement of the extramural cancer community in research directed toward the unique etiologic and pathogenic features of these malignancies, NCI recently issued and funded two Requests for Application (RFAs), "Viral Etiology of AIDS-Associated Malignancies" and "Immunobiology of AIDS Lymphomas." The development of formal programs within NCI Cancer Centers dedicated to research on AIDS-related malignancies, the establishment of a multi-state AIDS/cancer match registry and the creation of a tissue and biologic fluids bank for HIV-associated malignancies will provide critical infrastructures for molecular studies that, in turn, will serve as the foundation for design of novel strategies aimed at therapy and prevention of AIDS-related malignancies. In this regard, NCI has recently issued an RFA to establish an AIDS Malignancy Clinical Trials Consortium in 1996 (using the U01 mechanism). This multi-institutional network will serve to design and conduct of innovative, early phase clinical trials which may form the basis for larger trials. The aim is to fund approximately 8-10 applications to design and develop exploratory clinical trials with novel agents and/or modalities in patients with AIDS-related malignancies in a collaborative, inter-institutional setting. Additionally, there will be 1 operational center funded for the purpose of data management and monitoring oversight. The resultant consortium will also provide tissues and biological fluids as a shared resource, and there are plans to have this consortium interface with the newly-formed tissue bank. NCI's Cancer Cooperative Groups conduct developmental clinical trials in AIDS-KS, anogenital malignancies and AIDS lymphomas (including Primary Central Nervous System Lymphomas).

The identification of lymphocytotoxic compounds for testing in AIDS lymphomas and, through developmental "mechanism of action" assays, cytokine inhibitors for potential application in AIDS and AIDS-related malignancies (for example, anti-angiogenesis agents in KS, biomodulation using retinoids plus interferon in cervical cancer) are important investigative directions. As one recent case in point, NCI has facilitated the preclinical evaluation and initial clinical testing of the anti-angiogenesis agent TNP-470 (a Fumagillin analog) for the treatment of patients with AIDS-KS. In addition, certain agents developed by NCI in its cancer drug programs are being adapted to KS and other AIDS-related cancers. As a key example, Taxol -- the tubulin-binding natural product with important clinical activity against many malignancies (e.g. ovarian, breast, bladder, head and neck, lung cancers) -- is demonstrating remarkable activity in KS, with a 65 percent response rate, including patients with pulmonary involvement. Adapting animal models, e.g. the SCID mouse, and the development of KS-derived spindle cell lines for preclinical drug evaluations are fundamental program efforts as well. To this end, NCI investigators have established and are molecularly characterizing six AIDS lymphoma cell lines for the purposes of targeted drug development; to date, over 1,000 agents have been screened *in vitro* and more than 70 agents are being tested against these human AIDS lymphomas *in vivo* (human lymphoma cells engrafted in SCID mouse), with excellent anti-lymphoma activity detected for camptothecins and tubulin-binding agents (like Taxol) so far.

Thus, the current and future directions of NCI's AIDS research span the broad spectrum of biologic and societal issues surrounding this disease, and command intensive commitment of resources. The pursuit of knowledge in virtually every phase of NCI's AIDS investigation is conducted in cooperation with efforts of the OAR to coordinate trans-NIH and trans-Public Health Service initiatives and the close collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and other sister agencies of government.

APPLICATION TO OTHER CANCER RESEARCH:

Regarding to what extent the knowledge gained in AIDS and breast cancer research may be beneficial and have applicability to other aspects of cancer research, we feel there is a cross-pollination. AIDS and breast cancer are devastating diseases that, at present, pose surpassingly important challenges to all domains of biomedical research. While we have a great distance to go toward the eradication of death and suffering from AIDS and breast cancer, the broad spectrum of basic and clinical research is beginning to change the face of both diseases. Major contributions to our basic understanding and clinical approaches to AIDS, breast cancer specifically and cancers in general have emerged from genetic studies in bacteria and fruit flies, studies of cell cycle regulation in yeast and amphibians, dissection of apoptosis in roundworms, and isolation and characterization of the multidrug resistance gene and protein in bacteria. Below is a brief encapsulation of selected areas where the bidirectional flow of information between AIDS research and cancer research have enriched our knowledge and influenced our interventional approaches to both diseases.

The interface between AIDS research and cancer research is extensive and cuts across all basic and clinical disciplines of biomedical research. Indeed, the foundation for much of AIDS research is a direct outgrowth of many areas of cancer research, in particular the study of genetic or iatrogenic immunodeficiencies and the entire discipline of retrovirology and viral carcinogenesis. In turn, the dissection of HIV immunopathogenesis has informed our understanding of critical components that come in to play in net tumor cell survival and the process of programmed cell death (apoptosis), tumor immunobiology and vaccine development. The cross-pollination between the Cancer and AIDS Drug Screen is a prime example. The knowledge gained from the basic and clinical investigation of AIDS-related Kaposi's sarcoma (KS) informs the entire field of research on new blood vessel development (angiogenesis) and the design and testing of new anti-angiogenesis agents for cancer. What is learned about the pathogenesis, pathopysiology and drug responsiveness of AIDS-related lymphomas has major implications for our understanding of non-HIV-related lymphomas in general. The same principle holds true for the human papilloma virus (HPV)-related anogenital malignancies that arise with increased frequency and severity in the HIV-infected host; indeed, HIV-infected individuals may constitute an important population for testing of HPV vaccines.

What is learned about one type of cancer can often be applied to our understanding of other cancers. The similarities of basic, population-based and clinical research approaches to breast, prostate, bowel and lung malignancies are noteworthy, and reflect a unity that underlies the development and progression of cancer. In particular, the knowledge gleaned about the etiololgy, epidemiology, biology, detection/diagnosis, treatment and prevention of breast cancer will have special relevance for other hormonally-driven cancers, namely prostate, ovarian, endometrial and perhaps even colon cancers. Thus, issues surrounding breast cancer transect and inform all aspects of cancer research. Further, breast cancer -- indeed, all cancers -- benefit from advances in knowledge emanating from basic mechanistic research. Perhaps a key example is the recent discovery of the "Breast Cancer-1" (BRCA-1) gene, which appears to be linked to ovarian, prostate and colon cancers as well as breast cancer. The multi-step hypothesis, so elegantly dissected for colorectal cancers, is now being unraveled for breast cancer as well. The emerging scientific, ethical and societal issues surrounding the genetic screening for BRCA-1 mutations and the implications that such screening has regarding multiple facets of medical care are a template for other inherited cancer predispositions. The Long Island Breast Cancer Study Project stands as a paradigm for molecular epidemiologic studies of environmental/occupational carcinogenesis. The large-scale Breast Cancer Prevention Trial (BCPT) is a ground-breaking study of hormonally-based chemoprevention that stands as a prototype for the landmark Prostate Cancer Prevention Trial (PCPT) and prevention trials for other malignancies that are under development or will be developed in the future. Breast cancer is an important testing ground for therapeutic strategies aimed at cure. This principle is exemplified by the approaches to adjuvant therapy in the so-called minimal residual disease state that have been developed and refined for breast cancer and now serve as templates for similar approaches in other cancers. In addition, the extrapolation and application of dose-intensive chemotherapies coupled with bone marrow reconstitution and hematopoietic growth factors (first pioneered in hematopoietic malignancies) to solid tumors has been pioneered in breast cancer. The expanding body of knowledge concerning the importance of angiogenesis in the clinical behavior (in particular, tumor dissemination) and overall prognosis of breast cancer, especially early-stage breast cancers, will inform our understanding and the design of therapeutic interventions in the many malignancies (prostate, ovarian, brain, bladder, gastric, to name a few) where angiogenesis plays a role in clinical tumor biology.

So, in sum, the lessons learned from AIDS and breast cancer research in the laboratory and in the clinic are critical building blocks for our developmental approaches in multiple arenas -- early detection and diagnosis, vaccine development, treatment and prevention. These lessons are instructive for the wide array of malignancies that arise in a myriad of settings, including the setting of HIV infection. The preservation and enhancement of the fluid exchange of information among the diverse disease entities and between the laboratory bench and the clinical arena are critical to our ability to capitalize on the advances that are now emerging to change the face of many cancers and AIDS from devastating and fatal to ultimately curable and perhaps preventable diseases.

APPLICATIONS OF AIDS AND BREAST CANCER RESEARCH

Mr. Stokes: To what extent has knowledge gained in AIDS research and breast cancer research had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your Institute?

Dr. Sondik: AIDS and breast cancer are diseases that, at present, pose surpassingly important challenges to all domains of biomedical research. While we have a great distance to go toward the eradication of death and suffering from AIDS and breast cancer, the broad spectrum of basic and clinical research is beginning to change the face of both diseases. Major contributions to our basic understanding and clinical approaches to AIDS, breast cancer specifically and cancers in general have emerged from genetic studies in bacteria and fruit flies, studies of cell cycle regulation in yeast and amphibians, dissection of apoptosis in roundworms, and isolation and characterization of the multi-drug resistance gene and protein in bacteria. Below is a brief encapsulation of selected areas where the bi-directional flow of information between AIDS research and cancer research have enriched our knowledge and influenced our intervention approaches to both diseases.

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So, in sum, the lessons learned from AIDS and breast cancer research in the laboratory and in the clinic are critical building blocks for our development approaches in multiple arenas -- early detection and diagnosis, vaccine development, treatment and prevention. These lessons are instructive for the wide array of malignancies that arise in a myriad of settings, including the setting of HIV infection. The preservation and enhancement of the fluid exchange of information among the diverse disease entities and between the laboratory bench and the clinical arena are critical to our ability to capitalize on the advances that are now emerging to change the face of many cancers and AIDS from devastating and fatal to ultimately curable and perhaps preventable diseases.

CHILDREN AND CANCER

Mr. Stokes: What is the extent of cancer in children and are we having much progress in treating and preventing cancer in children and adolescents?

Dr. Sondik: Cancer remains a major cause of mortality among children, and is the second leading cause of deaths beyond the perinatal period. The table below from the National Center for Health Statistics: Vital Statistics of the United States, lists the major causes of death among children ages 1-14 years old.

Cause	Deaths in 1990 in US	Percent
Accidents	6,216	40%
Cancer	1,607	10%
Congenital anomalies	1,364	9%
Homicide	890	6%
Heart diseases	590	4%
Pneumonia, influenza	305	2%
Cerebral palsy	303	2%
All Causes	15,367	100%

Approximately 8,000 children under 15 years of age are diagnosed with cancer each year in the United States, with another 2,000 cases of cancer occurring annually in the 15-19 year old age group.

A number of different types of cancer occur among children, and constitute a very different group of malignancies than those that occur in adults. The most common type of cancer occurring in children is leukemia, with 2,500 cases being diagnosed annually in the United States (2,000 cases of acute lymphoblastic leukemia and 500 cases of acute myeloid leukemia). Tumors of the brain (of which there are many different types) constitute the largest group of solid tumors among children, with approximately 2,000 cases diagnosed each year. The most common pediatric tumors, and the estimated number of cases each year among children under 15 years of age from SEER Program 1989-90 incidence data, are shown below.

Pediatric Type of Cancer	Estimated Cases Per Year	Percent
Acute lymphoblastic leukemia	2,000	25%
Central nervous system	1,800	22%
Neuroblastoma	580	7%
Kidney tumors	500	6%
Acute myeloid leukemia	500	6%
Non-Hodgkin's lymphoma	450	6%
Soft tissue sarcoma	450	5%
Bone tumors	340	4%
All Cancers	8,000	100%

A comparison of the number of cases of cancer diagnosed each year in the under 15 year old group (i.e., 8,000) to the number of deaths from cancer in the same age group (i.e., approximately 1,600) indicates that a large number of children are long-term survivors of their cancer.

Comparison of the 5-year relative survival rates for children diagnosed in the years 1974-76 to children diagnosed in the years 1983-89 shows that improved outcome has been obtained for most tumor sites. The table below shows 5-year survival rates by disease site for these time periods. Sites with significant improvements in outcome between the earlier and later time periods are indicated with an asterisk.

Pediatric Cancer Type	Percent of Total Cancer Cases	5 Year Survival Rates 1974-76	83-89
Acute lymphoblastic leukemia*	25%	52.5%	72.4%
Central nervous system*	22%	53.7%	59.9%
Neuroblastoma	7%	51.8%	56.7%
Kidney tumors (Wilms')*	6%	74.3%	88.4%
Acute myeloid leukemia*	6%	14.1%	31.1%
Non-Hodgkin's lymphoma*	6%	44.1%	67.6%
Soft tissue sarcoma	6%	60.7%	69.9%
Hodgkin's disease*	5%	78.3%	88.3%
Bone tumors	4%	54.3%	58.3%
All Sites	100%	55.2%	67.6%

For tumors such as Wilms' tumor and Hodgkin's disease, the vast majority of children are cured. For children with acute lymphoblastic leukemia, approximately three-fourths are 5-year survivors. For other cancers, such as acute myeloid leukemia, 5-year survival rates are well below 50%.

A major ongoing clinical research effort is being conducted by the National Cancer Institute to further improve outcome for children with cancer, especially those whose survival rate remains below 50%. Approximately 4,000 children are entered onto NCI-sponsored clinical trials annually. Among the strategies under evaluation in these NCI-sponsored trials are the following:

Application of this strategy resulted in improved outcome for children with ALL during the 1980's, and current studies are evaluating even more intensive therapies. This strategy is being applied not only for the leukemias, but also for solid tumors such as Ewing's sarcoma and rhabdomyosarcoma.

Clinical trials are being conducted of agents with new mechanisms of killing cancer cells that are completely different from those currently used in leukemia treatment. Examples include: (i) taxol and taxotere; and (ii) topotecan and 9-aminocamptothecin (topoisomerase-I inhibitors)

The myeloblative treatment strategies category includes bone marrow transplant studies. Allogeneic (i.e., matched sibling) bone marrow transplantation is under evaluation for "high-risk" ALL and also for children with AML. Autologous bone marrow transplantation, including the use of new purging methods to clear leukemia cells from the marrow before re-infusing the marrow, is under evaluation for children with AML and for some solid tumors. Studies of bone marrow transplant using matched unrelated donors are also planned for children with ALL. A common need for all of the transplant studies is better anti-leukemia chemotherapy (i.e., preparative regimens), because the stem cell transplants (especially autologous transplants) are basically ways to give chemotherapy that would otherwise be fatal. If the chemotherapy is inadequate, then the likelihood of benefit from the transplant is greatly reduced.

"Biologic" agents, such as Interleukin-2 (IL-2), may act by enhancing the ability of the immune system to recognize and kill leukemia cells Small pilot studies of IL-2 for children with AML are ongoing, and a large study is planned testing whether IL-2 treatment improves outcome when it is given after the completion of standard chemotherapy.

Targeted therapies take advantage of specific abnormalities in cancer cells that are not found in normal body cells. This area is especially important for improving the treatment of children with cancer. Our current therapy is like bombs that kill both normal and cancer cells. The targeted therapies would be more like "cruise missiles", able to identify specific targets and destroy them.

This targeted strategy is especially important in children, since the destruction of normal tissues can result in lasting detrimental effects (e.g., to the nervous system, the heart, the lungs). Among these strategies are monoclonal antibodies, that are able to specifically bind to and kill leukemia cells. Another strategy is to target the specific genetic causes of childhood leukemia, since these genetic changes differentiate the cancer cells from normal cells.

The problem of preventing childhood cancers is complicated by the lack of clearly identified etiologic agents for most childhood cancers, in spite of a number of epidemiological studies that have studied pediatric cancer patients and their families. Some cancers of childhood clearly have a genetic component (e.g., retinoblastoma), but these account for only a minority of patients. Children who are cured of their primary cancer may be at increased risk for developing a second cancer because of the treatment given for their primary tumor. A major effort has gone into identifying cancer treatments that are less likely to induce second cancers, and clinical trials have been conducted to maintain a high cure rate while using therapies that minimize the risk of a subsequent cancer developing. For example, radiation therapy, which can cause CNS tumors and bone tumors, is used much less commonly in current treatment protocols compared to 10 years ago for children with leukemia, without an adverse impact on the effectiveness of the leukemia therapy.

MINORITY HEALTH

Mr. Stokes: As I am sure you are aware, the disparity in minority health continues. In fact, the Assistant Secretary for Health in testimony before the committee this year indicated that the Department is enhancing its efforts to close the health disparity gap. While this issue is complex and a multiplicity of factors contribute to the disparity including life style and access to health care, biomedical research does have a key role to play in helping to close the gap. What can you tell us this year about improvements in minority health as a result of the research conducted by your Institute that you could not tell us when you were here last year?

Dr. Sondik: The charge of the National Cancer Institute is to carry out a comprehensive program of research and application to find the means to reduce the burden of cancer. The program developed to meet this challenge includes research on cancer risk factors, advancement of treatment and diagnosis, and development of prevention and control methods, as well as the design of effective strategies for information dissemination to the public and the nation's health professionals. The means to accomplish these tasks in minority populations addressed are many and include two categories of projects: (1) projects targeted to special populations; and (2) projects targeted to issues, tumor types, or problems that differentially affect a special population but are applicable to the general population.

A third category of projects is also central to the NCI effort to ensure that all Americans benefit from the National Cancer Program. This category contains the broad-based programs that are not targeted specifically to the special populations, or to the issues affecting them disproportionately, but nevertheless include and encourage their participation. Examples of these projects include the American Stop Smoking Intervention Trial (ASSIST) and the 5-A-Day for better health program. As another example, the NCI administers a human tissue procurement network to provide cancer tissues to scientists investigating putative risk factor markers. This is an important resource for investigators looking for molecular markers and comparing their expression in tumors that have a disproportional impact on minority populations. In addition, the NCI supports and participates in broad national efforts, such as the meetings of the President's Cancer Panel, to examine the current challenges to cancer researchers.

In the area of clinical research, overall policy requires that applicants for clinical research grants and cooperative agreements include minorities in study populations. Racial, ethnic, and gender issues must be addressed in the development of the research design and sample size, and the rationale for selection of the proposed study population included in the application. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups.

Lung cancer rates in men, including African American men appear to be leveling off and there is some indication that incidence rates are declining.

In response to the dramatic increase in prostate cancer incidence rates the NCI has initiated a Surveillance, Epidemiology and End Results (SEER) special study involving 5,000 men in six SEER areas with an oversample of African American and Hispanic men. The focus of the study is to examine patterns of health care and associated treatment sequelae as well as quality of life.

Colon cancer mortality rates have been declining and we have observed a leveling off in African American women. Current research efforts include an in-depth analysis of possible screening effects and clinical management.

The NCI recently funded cooperative agreements to examine breast cancer screening and physician decision making focusing on minority populations.

Complete data on minority health are not yet available but are expected this Fall. It is fair to assume, however, that there will be little change in improvements in minority health from the last time we presented data. It is important to note that NCI has expanded it's surveillance efforts in tracking cancer rates for minorities as well as data sets related to causative factors such as access to health care. These data will provide important clues in understanding differences in cancer rates and ultimately provide a blueprint for research and intervention.

An NCI report describing initiatives for minority populations for the years 1993 - 1994 is available to the public and can be obtained from the National Cancer Institute, Office of Cancer Communications.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of Research Project Grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the FY 1996 budget would support a success rate of 23 percent. If we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten to fifteen years, explain.

Dr. Sondik: The total number of NCI research project grant awards, both competing and non-competing, remained fairly constant, at about 3,000 awards from 1985 to 1991. Since FY 1992, numbers of total RPGs have grown to approximately 3,300 grants each year.

From FY 1985 to FY 1994 the number of submitted competing applications has increased by 23 percent. Success rates for NCI in total have fluctuated from a high of 34 percent to a low around 22 percent. NCI's overall success rates are estimated to be about 20% in both FYs 1995 and 1996.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Sondik: The average cost of NCI RPGs, according to data provided by the NIH Division of Research Grants, has increased a total of 54.8 percent in that ten year period. In 1985, the average cost was $167,898, which increased to $220,504 by 1989, a total growth of approximately 31.3 percent. Average cost continued to grow during the next five years, but at a smaller rate, reaching $260,001 in 1994, a growth rate of only 17.9 percent over 1989.

In terms of constant dollars, using FY 1985 as the base and the Biomedical Research and Development Price Index (BRDPI) as the inflation index, the average annual cost of research project grants has increased over the 10 year period by approximately 3 percent. From 1985 to 1989, the increase was about 8 percent, but since 1989, average cost in constant dollars has declined about 5 percent.

SUCCESS RATE OF MINORITY RESEARCH APPLICATIONS

Mr.Stokes: What is the success rate for research applications received from minority researchers?

Dr. Sondik: To comply with federal mandates, all questions related to race and gender are identified as optional on all NCI research grant applications. As a result, NCI is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. Also, on average, approximately 5 percent of grant applicants choose not to complete the portion of the grant application referring to race and gender and have been coded in the "unknown" category. There is no way to predict the race or gender composition of those applicants. Thus, the following NIH Division of Research Grants data may not provide a true representation of NCI's support of minority and women researchers.

The following table lists success rates for minority researchers for FY 1994, including a category identified as "unknown" for those grant applicants who chose not to identify their ethnic origin and/or gender. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NCI's support:

Competing Grant Success Rates for Minority Researchers
Total NCI
Fiscal Year 1994

Asian	African-Amer.	Hispanic	Native Amer.	Unknown	White
17.9%	10.0%	23.6%	25.0%	27.0%	21.0%

Mr. Stokes: What is the success rate for research applications received from women?

Dr. Sondik: The following DRG data identifies success rates for women researchers who chose to answer the optional questions on the grant application related to race and gender. A category denoted as "unknown" represents success rates for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NCI's support of women researchers:

Competing Grant Success Rates for Women Researchers

Total NCI
Fiscal Year 1994

Female	20.3%
Unknown	28.0%

Mr. Stokes: What is the success rate for research applications received from African American?

Dr. Sondik: The following DRG data identifies success rates for researchers of African American descent who chose to answer the optional questions on the grant application related to race. A category denoted as "unknown" represents success rates for applications in which race could not be determined. Since there is no way to predict the composition of the applicants in the "unknown" category the following data may not provide a true representation of NCI's support of African American researchers:

Competing Grant Success Rates for African American Researchers
Total NCI
Fiscal Year 1994

African-American	10.0%
Unknown	27.0%

Mr. Stokes: What is the success rate for research applications received from HBCUs?

Dr. Sondik: Historically, the NCI received fewer than 20 competing applications from HBCUs; in the recent past the range of applications funded has varied from none to four.

AVERAGE COST OF RPGs TO WOMEN AND MINORITIES

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to women?

Dr. Sondik: The following NIH Division of Research Grants (DRG) data identifies the average cost of competing awards to women researchers in real and constant dollars. As stated previously, questions related to race and gender are optional on NCI grant applications. As a result, the following table identifies a gender category denoted as "missing" which represents the average cost of competing grants for applications in which gender could not be determined. Since there is no way to predict the composition of the applicants in the "missing" category the following data may not provide a true representation of NCI's support of women researchers:

Competing Grant Average Costs for Women Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NCI:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Women	$139.8	$139.8	$165.1	$136.2	$226.5	$150.6
Missing	158.0	158.0	196.3	162.0	200.6	133.4

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to minority researchers?

Dr. Sondik: The following data identifies the average cost of competing awards to minority researchers in real and constant dollars. As stated previously, questions related to race are optional on NCI grant applications. As a result, the following table identifies a race category denoted as "missing" which represents the average cost of competing grants for applications in which the ethnicity of the awardee is undetermined. Since there is no way to predict the composition of the applicants in the "missing" category the following data may not provide a true representation of NCI's support of minority researchers:

Competing Grant Average Costs for Minority Researchers in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NCI:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Asian	$123.4	$123.4	$158.9	$131.1	$210.0	$139.7
Black	139.2	139.2	271.9	224.3	173.8	115.5
Hispan.	166.9	166.9	422.0	348.2	170.4	113.3
N.Amer.	No Awards		151.2	124.8	243.1	161.7
Missing	198.9	198.9	190.2	156.9	272.2	181.0
White	172.3	172.3	224.7	185.4	263.6	175.3

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to African American researchers?

Dr. Sondik: As shown in the previous table, the average cost of awards to African American researchers in constant and current dollars are as follows:

Competing Grant Average Costs for African American Researchers
in Current and Constant Dollars

In Five Year Increments FY 1985, FY 1989, and FY 1994
Total NCI:
(Dollars in thousands)

	1985		1989		1994	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
Black	$139.2	$139.2	$271.9	$224.3	$173.8	$115.5
Missing	198.9	198.9	190.2	156.9	272.2	181.0

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average costs of Research Project Grants awarded to HBCUs?

Dr. Sondik: According to NIH Division of Research Grants data, there were no competing NCI awards to Historically Black Colleges in 1985, 1989, or 1994. Awards were made in 1986, 1987, 1991, 1992, and 1993, however. Average costs for selected years, in real and in constant dollars (using 1985 as the base), are as follows:

Competing Grant Average Costs for HBCUs
in Current and Constant Dollars

Selected Years, 1986 - 1993
Total NCI:
(Dollars in thousands)

	1986		1991		1993	
	Current	BRDPI	Current	BRDPI	Current	BRDPI
HBCUs	$94.1	$90.3	$381.3	$284.4	$213.8	$147.7

ENVIRONMENTAL JUSTICE INITIATIVE

Mr. Stokes: I understand that the Secretary of the Department of Health and Human Services has submitted an Environmental Justice Strategic Plan to the White House. Low-income and minority communities suffer a disproportionately higher rate of cancer, lead-poisoning, and asthma than the general population, much of which is associated with environmental hazards. The National Institute on Environmental Health Sciences has developed an environmental justice researchers, health care providers, and community-based partnership program to more effectively address this national health problem.

What is the Cancer Institute's role in the Department's Environmental Justice initiative; more specifically, how does the NCI plan to implement the Departmental strategy on environmental justice? How much is included in the FY 1996 budget request with respect to this initiative?

Dr. Sondik: NCI is engaged in a number of initiatives which address the Departmental strategy on environmental justice, in particular its first goal, i.e., to focus attention on the human health and environmental conditions in minority and low-income communities. One example of such an initiative, which involves multiple agencies, is the proposed Triana, Alabama study of DDT exposure and breast cancer risk.

Triana is a small rural town adjacent to Redstone Arsenal whose residents are primarily low-income African-Americans and whose livelihoods once depended on commercial fishing. It is located at the confluence of the Tennessee River and Indian Creek. From around 1947 until the early 70s, a chemical factory located at Redstone Arsenal discharged approximately 400 tons of DDT and associated waste into local waterways, leading to contamination of Indian Creek and the Tennessee River. Monitoring activities by the Centers for Disease Control (CDC) revealed high levels of DDT contamination of fish in Indian Creek and the Tennessee River and high body burdens of DDT in inhabitants of Triana, probably due to ingestion of contaminated fish. A subsequent lawsuit by residents of Triana was settled and the court, in 1983, established the Triana Area Medical Fund to provide for the medical and other needs of citizens with high body burdens of DDT. Court-ordered remediation efforts were initiated in the early 1980s and their progress monitored by the US Environmental Protection Agency and the Tennessee Valley Authority. Currently, a court-ordered follow-up health survey is being completed on all participants to augment medical and insurance claims data, which will be used to provide a 10-year report to the Federal District Court.

The heavy exposure and high body burdens of DDT, the availability of previously collected information on some subjects, including blood and adipose tissue samples, and support from the Triana Area Medical Fund Board make this a unique and promising population for a study of the possible relationship between exposure to DDT and breast cancer risk. For this reason NCI scientists, in collaboration with the University of Alabama College of Nursing and with the Triana Area Medical Fund Board, is planning to carry out an investigation on the relationship between tissue levels of DDT and the risk of breast cancer and breast disease within this well-characterized population using previously collected blood samples. Mammography screening will be provided gratis to the Triana cohort to identify women with previously undetected breast cancer, benign breast disease, or who have dense breast tissue. Serum levels of DDT from samples drawn at the time of mammographic screening from these women will also be compared to serum levels from 1979 to identify factors which may influence changes in DDT levels over time.

In parallel studies, NCI scientists are collaborating with staff from the Tennessee Valley Authority and the Environmental Protection Agency to sample fish from Indian Creek and the Tennessee River for DDT residues in flesh and fish-growth parameters, and these analyses are underway. Concomitantly, NCI staff and staff from the NCI-supported Registry of Tumors in Lower

Animals at the Smithsonian Institution are examining these fish for external and histopathologic evidence of tumors. The current funding level for these projects is approximately $275,000, and an additional $500,000 is requested for FY 1996 through the National Action Plan for Breast Cancer to implement the mammography screening initiative.

Mr. Stokes: Are other Institutes such as the National Heart, Lung, and Blood Institute, and the National Institute on Allergy and Infectious Diseases participating in this initiative?

Dr. Sondik: The National Institute of Environmental Health Sciences at NIH is spearheading the Agency's involvement in the Department's Environmental Justice Initiative. As NIH's lead Institute on this initiative, NIEHS is working with NCI, the NIH Office of Minority Health, and other Institutes. NIEHS is also cooperating with the Environmental Protection Agency; the National Institute for Occupational Safety and Health, CDC; the Agency for Toxic Substances and Disease Registry; the Department of Energy; and the National Center for Environmental Health, CDC.

PANCREATIC CANCER

Mr. Hoyer: Any type of cancer is a serious illnesses, but pancreatic cancer is even more deadly than many, with most patients dying within months of diagnosis. Could you update the committee on the status of your research and the prospects for achieving them?

Dr. Sondik: Pancreatic cancer is emblematic of the challenge of cancer research. In 1995, it is estimated that 24,000 people will develop pancreatic cancer and 27,000 will succumb to the disease. Indeed, pancreatic cancer is the fifth leading cause of cancer-related deaths in the United States. Both the incidence and mortality have changed relatively little over the last two decades, although there appears to be a slight but consistent downward trend in both incidence and mortality (about 1 percent per year) in white men under the age of 65. Sadly, both the incidence and mortality are higher in African Americans than in whites by approximately 50 percent. At present, only 3.6 percent of all patients with pancreatic cancer will survive 5 years, and the median survival is less than 1 year. As for other malignancies, the survival is somewhat better for those who have localized disease at the time of diagnosis (11 percent 5-year survival) than for those with distant disease (1.6 percent 5-year survival). However, pancreatic cancer is often clinically silent for prolonged periods, until such time as the tumor mass produces clinical symptoms such as jaundice from biliary obstruction or hepatic infiltration, abdominal pain and severe wasting. Indeed, about 50 percent of all cases of pancreatic cancer present with disseminated (metastatic) disease and 25 percent present with regional lymph node involvement; only 8 percent of all pancreatic cancer patients present with localized (early stage) disease.

The National Cancer Institute (NCI) supports a broad portfolio of multidisciplinary research aimed at understanding the etiology and improving the diagnosis, treatment and prevention of pancreatic cancer. Indeed, pancreatic cancer research is a cornerstone of the NCI Gastrointestinal (GI) Malignancies Specialized Program of Research Excellence (SPORE), located at the Johns Hopkins Oncology Center. In 1996, NCI proposes to support an additional 1-2 GI SPOREs, with an emphasis on pancreatic cancer. There is a emerging understanding of the molecular foundations of pancreatic carcinogenesis (genetics, molecular epidemiology and biologic expression of disease) and, most recently, an increasing complement of agents under preclinical and clinical development that are directed toward these molecular targets. Given this burgeoning knowledge, NCI will conduct a meeting of intramural scientists from both NCI and the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) and extramural investigators (oncologists and gastroenterologists) in June 1995 to address and define the possibilities for rapid translation of the basic and preclinical discoveries into the clinical testing arena.

Genetic linkage studies have shed light on the inheritance of predisposition to pancreatic cancer. In fact, predisposition to pancreatic cancer is an integral part of Hereditary Non-Polyposis Colorectal Cancer (HNPCC), an inherited syndrome characterized by defects in one of a complex of four "mutator" or "master" genes that normally act to repair errors in DNA replication -- so-called, mismatch DNA repair. This 4-gene complex was discovered as a direct outgrowth of studies in bacteria. Mutations in any one of these genes cause "proofreading" errors in DNA which, in turn, leads to instability and genetic alterations throughout the cell's genetic material. Hereditary defects in the mismatch DNA repair gene complex are associated with several gastrointestinal cancers -- colorectal, gastric and pancreatic -- and are also linked to heightened risks for endometrial, bladder and perhaps ovarian and breast cancers as well. In addition, mutations of the ras oncogene are detected in the vast majority (90 percent) of pancreatic cancers and may play a fundamental role in the early phases of tumorigenesis. Such mutant ras genes are also detectable in stool samples obtained from patients with pancreatic cancer, and this important finding forms the basis for a practical and non-invasive method for pancreatic cancer detection and diagnosis.

Several environmental/occupational factors may induce or promote pancreatic carcinogenesis. NCI-sponsored epidemiologic studies have demonstrated an association between pancreatic cancer risk and dietary factors such as high meat consumption (perhaps specifically the heterocyclic amines generated during high-temperature cooking of meats), high alcohol intake and heavy (more than 25 cigarettes daily) cigarette smoking. Other potential etiologic factors for pancreatic cancer are being examined in diverse epidemiologic studies, including NCI's large-scale Agriculture Health Study (being conducted in cooperation with the National Institute of Environmental Health Sciences and the Environmental Protection Agency). Such factors include solvents such as methylene chloride, pesticides, and infectious agents causing chronic pancreatitis, for instance cytomegalovirus.

In addition to the above-noted genetic abnormalities, NCI-supported scientists are dissecting the molecular composition of pancreatic cancer cells as a basis for designing novel vaccine constructs, diagnostic reagents and targets for therapy. To this end, the newly-uncovered cell surface protein known as CD44 is detectable both on pancreatic tumor cells and in the blood of patients with pancreatic cancer, and may thus serve as a tumor-associated marker for early, non-invasive diagnosis. In addition, CD44 may provide a target for monoclonal antibody (MoAb) development for the purposes of diagnosis and tumor-targeted therapies.

Pancreatic cancer provides a fertile testing ground for innovative cancer vaccines. One important vaccine target is the mutated ras oncogene, which produces mutant Ras proteins that are capable of engendering an immune response. In this light, intramural and NCI-sponsored extramural scientists are developing and clinically testing Ras vaccine constructs (in particular patient-specific synthesized mutant Ras peptides) in patients with pancreatic cancer and other cancers where ras mutations have likely pathogenic roles, for instance colon and lung cancers. Another tumor-associated antigen, the mucin known as MUC-1, present on both pancreatic and breast cancer cells, is being exploited for its potential as a vaccine candidate; indeed, MUC-1 vaccines are currently in clinical testing in both breast and pancreatic cancers. The CD44 protein discussed above may also serve as a future vaccine candidate. In addition, based on their pioneering preclinical and early clinical studies of gene therapy-based vaccines in kidney cancer and now in prostate cancer, investigators at the Johns Hopkins Gastrointestinal SPORE are developing a similar vaccine construct for pancreatic cancer -- namely, the alteration of pancreatic cancer cells by introducing the gene encoding the growth factor known as Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), a manipulation that renders the tumor cells more immunogenic and therefore more susceptible to destruction by tumor-targeted immune cells.

To date, the systemic (non-surgical) therapy of pancreatic cancer has yielded very frustrating results. Now, however, there are a number of novel approaches that are currently in (or about to enter) clinical testing. For example, an approach pioneered by NCI investigators involves the modulation of an intracellular enzyme (thymidylate synthase) by leucovorin and interferon that enhances the cytotoxicity of the antimetabolite drug 5-fluorouracil (5-FU). This approach has been found to have significant antitumor effects in refractory colorectal cancers and, preliminarily, in metastatic pancreatic cancers as well. Another class of agents that hold promise for pancreatic cancer are the agents that inhibit the net expression of ras. Some of these agents are already in clinical trial in other ras-overexpressing cancers such as glioblastoma and prostate cancer. Such agents include the isoprenylation inhibitors such as lovastatin, phenylacetate, limonene and perillyl alcohol, each of which acts to block the attachment of Ras proteins to the cell membrane and thus the ability of Ras proteins to transduce biochemical signals from the cell membrane to the nucleus. Additionally, the novel anti-signaling drug known as CAI has major growth-suppressive effects against pancreatic cancer cell lines in the laboratory and is currently being studied in a Phase II clinical trial at NCI that includes patients with pancreatic cancer. Lastly, a new cytotoxic antimetabolite, gemcitabine, has been shown to have promising effects in early clinical trials in both non-small cell lung cancer and pancreatic cancer, and is under clinical development through NCI's Cancer Clinical Cooperative Groups.

Ultimately, the ability to identify those individuals who, by virtue of heredity or environmental exposure, are at high risk for the development of pancreatic cancer should translate into an ability to prevent the process of pancreatic carcinogenesis. To this end, the development of reliable biomarkers to measure individual risk and also to monitor the impact of either a therapeutic or prevention intervention is an important direction of NCI-supported investigation. The continuing elucidation of tumor-linked components -- for example, the identification of "mutator gene" abnormalities and detection of ras mutations in stool cytology or CD44 in blood -- and the understanding of the meaning of such changes in the context of pancreatic cancer evolution will provide the molecular tools to achieve the goal of cure and prevention of pancreatic cancer.

H. PYLORI

Mr. Hoyer: Research at the NIDDK and elsewhere has led to consensus that duodenal ulcers are largely caused by a bacterium, *H. pylori*. This finding has opened new prospects for a simple, inexpensive antibiotic treatment to address what has up until now been a costly condition. New possibilities, such as a link between *H. pylori* and stomach cancer and a preventive vaccine, have now opened up. Does the NCI have any plans for pursuing the link between *H. pylori* and cancer? How will your Institute work with the NIDDK to explore this possibility?

Dr. Sondik: In the ten years since *H. pylori* was first cultured and characterized, it has come under intense clinical scrutiny. There is now broad agreement that following infection, *H. pylori* colonizes the stomach and induces an acute inflammatory response. The bacteria remain active in the gastric epithelium for years (or possibly decades), giving rise over time to chronic gastritis with atrophy which serves as a critical first step in the progression of events that ultimately leads to the development of gastric cancer. In addition, the recent demonstration of an association between *Helicobacter* infection, reactive proliferation of mucosa-associated lymphoid tissue (MALT), and the occurrence of primary gastric B-cell MALT lymphoma in humans, as well as a report of neoplastic lesions in mice infected with a different species of *Helicobacter*, suggests a wider role of these organisms in cancer etiology.

Currently, NCI is investigating the incidence of *H. pylori* infection in epidemiologic studies. NCI is conducting a number of epidemiologic studies to further elucidate the role of *H. pylori* in gastric cancer. In Shandong Province, a rural area of northeast China where the stomach cancer rates are among the highest in the world, NCI's Epidemiology and Biostatistics Program has been collaborating with the Beijing Institute for Cancer Research since 1983 to assess the risk factors associated with this disease and to test various means for its prevention. Initial findings showed increased risks associated with consumption of salt and a fermented local food (i.e., sour pancakes), while reduced risks were related to intake of allium vegetables (e.g., scallions and garlic) and beta-carotene and vitamin C-containing fresh fruits and vegetables. In a gastroscopic screening program, chronic atrophic gastritis, an early precancerous lesion, was found in almost the entire adult population of this region. This screening program also found *H. pylori* infection linked to early stages of chronic atrophic gastritis and to its progression to more advanced disease.

In order to assess the current state of knowledge on the role of *H. pylori* in gastric cancer in humans, NCI sponsored an October 1993 workshop entitled "Helicobacter and Cancer." The recommendations made at the workshop led to a Request for Applications (RFA) entitled "The Role of *Helicobacter* in Cancer" jointly sponsored by NCI and NIDDK.

The overall goal of the RFA is to promote research which will define the mechanistic role of *Helicobacter* species in the etiology of cancer. Examples of relevant studies would include areas such as defining factors of the *Helicobacter* species that may contribute to carcinogenic potential; characterizing relevant animal models that will reflect development of *Helicobacter*-related neoplastic changes seen in humans; developing *in vitro* methods of culturing and propagating *Helicobacter* species without loss of animal pathogenicity; developing reagents or markers for early detection of precancerous lesions, such as atrophic gastritis, in humans or in animal models; and developing diagnostic tests and tools to isolate and identify *Helicobacter* serotypes and/or genotypes leading to or associated with cancer in humans.

The information and technologies derived from the research supported by this RFA will provide a foundation for identifying individuals at high risk for developing gastric malignancies (both adenocarcinoma and B-cell mucosa-associated lymphoid tissue, or MALT, lymphoma) or possibly other cancers that might be etiologically linked to *Helicobacter*. In turn, such individuals would be potential candidates for prevention clinical trials aimed at bacterial eradication and suppression of transformed cell clones, using newly uncovered biomarkers to quantitate and monitor risk and clinical response to intervention. Awards are expected in FY 1995.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

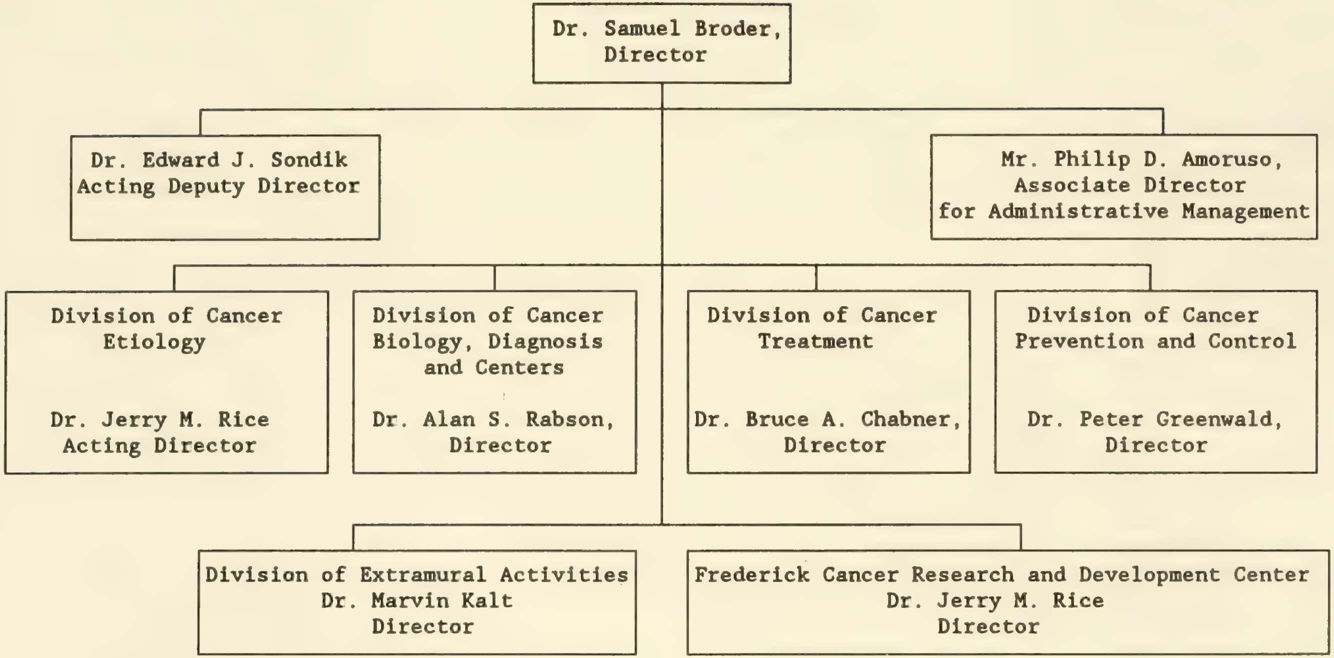
National Cancer Institute

FY 1996 Budget	Page No.
Organization chart	74
Appropriation language	75
Language analysis	76
Amounts available for obligation	77
Budget mechanism table	78
Summary of changes	80
Budget authority by object	82
Administrative costs	84
Significant items in House and Senate Appropriations Committee reports	85
Authorizing legislation	94
Appropriation history	95
Budget authority by activity	96
Justification:	
A. General statement	97
B. Cancer causation research	104
C. Detection and diagnosis research	109
D. Treatment Research	112
E. Cancer biology	116
F. Resource development: centers, manpower, construction	121
G. Cancer prevention and control	128
H. Detail of end-of-year employment	136
I. Detail of full time equivalent employment (FTE)	137

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and Title IV (excepting Section 417B(d)) of the Public Health Service Act with respect to cancer [$1,919,419,000] *$1,994,007,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Language Analysis

Language Provision	Explanation
"...(excepting Section 417B(d))..."	This language has been added to remove the requirement that NCI spend 10 percent of its total appropriation on cancer control activities.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation[1]

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation....................	$2,082,267,000	$1,919,419,000	$1,994,007,000
Rescission in accordance with PL 103-211................	-5,885,000		
Section 205 Procurement reduction......................		-1,482,000	
Section 207 Rent reduction........		-116,000	
Section 513 S&E reduction.........		-901,000	
Subtotal, adjusted appropriation	2,076,382,000	1,916,920,000	1,994,007,000
Comparative transfer to:			
Office of AIDS Research, NIH for HIV Activities.......	-213,017,000		
Comparative transfer from:			
Other NIH Institutes for Management Fund Adjustment...	+728,000	+984,000	
Subtotal adjusted budget authority	1,864,093,000	1,917,904,000	1,994,007,000
Unobligated balance lapsing.......	-164,000	---	---
Total Obligations................	1,863,929,000	1,917,904,000	1,994,007,000

[1] Excludes the following amounts for reimbursable activities carried out under this account: 1994 -- $10,856,000 and 7 FTEs; 1995 -- $12,000,000 and 15 FTEs; 1996 -- $15,000,000 and 15 FTEs.

Also excludes funding for HIV activities: FY 1995 -- $218,504,000; FY 1996 -- $225,790,000, included in the Office of AIDS Research, NIH.

Note: Excludes $6,185,000 for royalties in FY 1994 and $9,800,000 in FY 1995.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
Research grants	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting..................	2326	$665,008,000	2261	$671,162,000	2170	$663,961,000
Administrative supplementals..	(248)	10,963,000	(203)	12,500,000	(144)	10,480,000
Competing:						
Renewal....................	288	104,546,000	305	105,270,000	338	123,740,000
New........................	508	102,754,000	448	98,975,000	518	120,422,000
Supplemental...............	4	733,000	4	352,000	4	408,000
Subtotal, competing...........	800	208,033,000	757	204,597,000	860	244,570,000
SBIR/STTR.....................	179	22,773,000	162	31,925,000	284	40,074,000
Subtotal, research projects.	3305	906,777,000	3180	920,184,000	3314	959,085,000
Research centers:						
Basic research................	13	19,013,000	12	23,444,000	12	24,430,000
Clinical/comprehensive........	42	113,619,000	44	104,387,000	44	107,224,000
Subtotal, Core Grants.......	55	132,632,000	56	127,831,000	56	131,654,000
SPORE Grants..................	9	22,049,000	13	25,816,000	13	21,993,000
Subtotal, Centers and SPOREs	64	154,681,000	69	153,647,000	69	153,647,000
Other research:						
Research career program.......	187	14,299,000	191	14,386,000	197	15,242,000
Cancer education..............	75	8,183,000	73	7,904,000	78	8,662,000
Cooperative clinical research.	155	76,075,000	232	77,233,000	232	79,594,000
Minority biomedical research support............	---	3,070,000	---	3,099,000	---	3,316,000
Other research related........	86	5,519,000	141	5,569,000	141	5,569,000
Subtotal, other research....	503	107,146,000	637	108,191,000	648	112,383,000
Total, research grants...........	3872	1,168,604,000	3886	1,182,022,000	4031	1,225,115,000

Training:						
Individual awards:						
Noncompeting................	89	2,517,000	99	2,910,000	119	3,386,000
Competing...................	73	1,911,000	64	1,534,000	44	1,187,000
Subtotal, individual........	162	4,428,000	163	4,444,000	163	4,573,000
Institutional awards:						
Noncompeting................	1107	27,918,000	724	20,249,000	952	27,415,000
Competing...................	194	5,118,000	501	13,848,000	273	7,671,000
Subtotal, institutional.....	1301	33,036,000	1225	34,097,000	1225	35,086,000
Total, training..................	1463	37,464,000	1388	38,541,000	1388	39,659,000
Research & development contracts.	169	136,287,000	165	128,384,000	154	126,231,000
[SBIR contracts].............	(7)	(1,154,000)	(4)	(990,000)	(10)	(1,826,000)
	FTE		FTE		FTE	
Intramural research..............	1697	270,639,000	1652	279,576,000	1636	287,277,000
Research management and support..	516	89,000,000	477	88,998,000	465	90,455,000
Cancer prevention and control....	169	145,600,000	186	192,383,000	188	222,270,000
Construction.....................		16,499,000		8,000,000		3,000,000
Total, NCI.......................	2382	1,864,093,000	2315	1,917,904,000	2289	1,994,007,000
Clinical trials..................		(289,321,000)		(298,001,000)		(309,921,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

1995 Estimated budget authority	$1,917,904,000
1996 Estimated budget authority	1,994,007,000
Net Change	+76,103,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTE	Budget Authority	FTE	Budget Authority
A. Built - in:				
1 Intramural research:				
a. Within grade increase		$112,885,000		+$1,464,000
b. One more day of pay		112,885,000		+430,000
c. Annualization of Jan 1995 pay raise		112,885,000		+796,000
d. Jan 1996 pay increases		112,885,000		+1,847,000
e. Federal employees compensation fund, unemployment compensation		112,885,000		+13,000
f. Increased cost of centrally furnished services		92,711,000		+4,957,000
g. Federal telecommunications system savings		1,967,000		-22,000
h. Service & supply fund increase		16,950,000		+464,000
i. Increased cost of laboratory materials & other expenses		55,063,000		+1,643,000
Subtotal				+11,592,000
2 Research management & support:				
a. Within grade increase		27,988,000		+368,000
b. One more day of pay		27,988,000		+108,000
c. Annualization of Jan 1995 pay raise		27,988,000		+194,000
d. Jan 1996 pay increases		27,988,000		+465,000
e. Federal employees compensation fund, unemployment compensation		28,545,000		+4,000
f. Increased cost of centrally furnished services		12,349,000		+730,000
g. DHHS working capital fund		1,481,000		-231,000
h. Federal telecommunications system savings		7,176,000		-202,000
i. Service & supply fund increase		8,869,000		+229,000
j. Increased cost of laboratory materials & other expenses		31,135,000		+1,274,000
Subtotal				+2,939,000

Summary of Changes--continued

	1995 Current Estimate Base		Change from Base	
	No.	Budget Authority	No.	Budget Authority
3 Cancer prevention & control:				
a. Within grade increase....		$13,133,000		+$197,000
b. One more day of pay......		13,133,000		+58,000
c. Annualization of Jan 1995 pay raise..........		13,133,000		+104,000
d. Jan 1996 pay increases...		13,133,000		+249,000
e. Increased cost of centrally furnished services................		1,768,000		+77,000
f. Service & supply fund increase................		3,058,000		+31,000
g. Increased cost of laboratory materials & other expenses........		9,208,000		+264,000
Subtotal......................				+980,000
B. Program:				
1 Research project grants:				
a. Noncompeting............	2,261	683,662,000	-91	-9,221,000
b. Competing..............	757	204,597,000	+103	+39,973,000
c. SBIR/STTR..............	162	31,925,000	+122	+8,149,000
Subtotal................	3180	920,184,000	+134	+38,901,000
2 Research Centers:				
a. Basic research..........	12	23,444,000	0	+986,000
b. Clinical/comprehensive..	44	104,387,000	0	+2,837,000
Subtotal................	56	127,831,000	0	+3,823,000
c. SPORE grants............	13	25,816,000	0	-3,823,000
Centers & SPOREs.........	69	153,647,000	0	0
3 Other research...............	637	108,191,000	+11	+4,192,000
4 Research training............	1,388	38,541,000	0	+1,118,000
5 R&D contracts................	165	128,384,000	-11	-2,153,000
	FTE		FTE	
6 Intramural research..........	1,652	279,576,000	-16	-3,891,000
7 Research management & support....................	477	88,998,000	-12	-1,482,000
8 Cancer prevention & control................	186	192,383,000	+2	+28,907,000
9 Construction.................		8,000,000		-5,000,000
Subtotal......................		1,885,979,000		+60,592,000
Total, Changes................				+76,103,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....................	2,315	2,289	-26
Full-time equivalent of overtime and holiday hours....	17	17	---
Average ES Salary...............	$112,601	$115,078	+$2,477
Average GM/GS grade.............	10.6	10.6	---
Average GM/GS Salary............	$49,366	$51,504	+$2,138
Average Salary, grades established by act of July 1, 1944 [42 USC 207]....	$73,195	$75,537	--- +$2,342
Average salary ungraded positions............	$44,084	$45,495	+$1,411
Personnel compensation:			
Full-time permanent............	$82,605,000	$85,487,000	+$2,882,000
Other than full-time permanent.....................	18,099,000	18,722,000	+623,000
Other personnel compensation...	5,147,000	5,340,000	+193,000
Special personal services payments.............	19,531,000	20,283,000	+752,000
Total personnel compensation...	125,382,000	129,832,000	+4,450,000
Personnel benefits..............	28,352,000	29,337,000	+985,000
Benefits to former personnel....	272,000	271,000	-1,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Travel and transportation of persons....................	4,516,000	4,706,000	+190,000
Transportation of things........	841,000	902,000	+61,000
Rental payments to GSA..........	67,000	73,000	+6,000
Rental payments to others.......	535,000	559,000	+24,000
Communications, utilities, and miscellaneous charges......	8,666,000	9,014,000	+348,000
Printing and reproduction.......	6,338,000	6,672,000	+334,000
Other services:			
Consulting Services............	6,729,000	6,648,000	-81,000
Other services.................	31,371,000	35,034,000	+3,663,000
Purchases from Govt. Accts.....	155,519,000	164,281,000	+8,762,000
Operation of GOCOs.............	41,523,000	41,523,000	---
R&D Contracts..................	172,746,000	178,115,000	+5,369,000
Supplies and materials..........	23,717,000	24,279,000	+562,000
Equipment.......................	9,005,000	9,487,000	+482,000
Grants, subsidies, and contributions..............	1,301,748,000	1,352,673,000	+50,925,000
Insurance claims and indemnities	577,000	601,000	+24,000
Total authority by object......	1,917,904,000	1,994,007,000	+76,103,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Administrative Costs

	1995 Current Estimate	1996 Estimate	Increase or Decrease
Personnel compensation:			
Full-time permanent (11.1)..........	$82,605,000	$85,487,000	+$2,882,000
Other than full-time permanent (11.3)..................	18,099,000	18,722,000	+623,000
Other personnel compensation (11.5).	5,147,000	5,340,000	+193,000
Special personal services payments (11.8)............	19,531,000	20,283,000	+752,000
Total personnel compensation (11.9).	125,382,000	129,832,000	+4,450,000
Personnel benefits (12.0)...........	28,352,000	29,337,000	+985,000
Benefits to former personnel (13.0)..	272,000	271,000	-1,000
Travel and transportation of persons (21.0)..................	4,516,000	4,706,000	+190,000
Transportation of things (22.0)......	841,000	902,000	+61,000
Rental payments to others (23.2).....	535,000	559,000	+24,000
Communications, utilities, and miscellaneous charges (23.3)....	8,666,000	9,014,000	+348,000
Printing and reproduction (24.0).....	6,338,000	6,672,000	+334,000
Consulting Services (25.1)...........	2,974,000	2,946,000	-28,000
Other services (25.2)................	31,371,000	35,034,000	+3,663,000
Purchases from Govt. Accts (25.3)....	125,237,000	126,622,000	+1,385,000
Operation of GOCOs (25.4)............	12,269,000	12,269,000	---
Supplies and materials (26.0).........	23,092,000	23,628,000	+536,000
Total administrative costs..........	369,845,000	381,792,000	+11,947,000

National Cancer Institute
Significant Items in House, Senate and Conference Appropriations Committee Reports

Item FY 1995 House Report	Action Taken or to be Taken
Prostate Cancer	
1. The House in its report 103-553, page 46 states, "The Committee remains concerned that the incidence of prostate cancer continues to increase and encourages the NCI to expand its commitment to the prostate research program. During the hearings, NCI noted that African American males have a higher rate of prostate cancer than any other segment of the world's population. The Committee encourages NCI to place emphasis on research geared toward the development of effective early detection techniques and innovative treatments for the disease."	The Prostate Cancer Prevention Trial (PCPT) is testing the ability of Finasteride (Proscar) to reduce the incidence of prostate cancer. Black men and men with a family history of prostate cancer are being aggressively recruited for this trial, which will also evaluate the benefit of annual prostate examinations and serial prostate-specific antigen (PSA) blood tests for detection. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) is a clinical trial designed to determine whether the number of deaths can be reduced through early detection of these cancers. In a large study of tumors that occur excessively in African Americans, dietary intake of micronutrients, fruits and vegetables, fat, meat and alcohol are being examined. Also, questionnaire analysis from the Health Professionals' Follow-Up Study suggests that fat consumption (especially red meat) is directly related to prostate cancer risk. Basic scientists continue exploring the molecular and cellular events associated with prostate cancer. Investigators are studying molecular genetic and cytogenetic alterations in prostate tumors, including specific genes uniquely expressed in these tumors. Studies of tumor heterogeneity are working to insure accurate diagnosis and prognosis. A clinical study with prostate specific antigen (PSA) in a vaccinia vector has recently begun. Basic research targeted at identification of tumor

Item Prostate Cancer	Action Taken or to be Taken
	antigens has improved prospects for identification of antigens in prostate carcinomas. The NCI SPORE program (Specialized Programs of Research Excellence), intended to accelerate translational research, now includes two prostate cancer SPOREs. To complement these SPOREs, NCI is initiating planning this year for Prostate Cancer Research Programs in traditional Cancer Centers. In addition, the NCI is co-funding three O'Brien Urological Research Centers with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). These three centers are specifically addressing prostate cancer. Finally, a number of new chemoprevention clinical trials are planned to accelerate applied research in prostate cancer prevention.
Bionutrition	
2. The House in its report 103-553, page 46, stated, "The Committee was pleased to learn about the Institute's initiative to conduct research on the relationship between diet and cancer in African American Women. The Committee is looking forward to a progress report on the initiative at the 1996 appropriations hearings."	The NCI continues its commitment to research which examines the relationship between diet and cancer. Numerous multi-ethnic minority studies are examining ethnic diversity in diets and the risk of breast cancer. In addition, the role of diet is being analyzed in a large study of tumors that occur excessively in African Americans, including the intake of micronutrients, fruits and vegetables, fat, meat, and alcohol. In addition, NCI's Interactive Research Project Grants support interdisciplinary collaborative research to address the complex questions about quantifying the role of diet in cancer prevention. The NCI has also issued a request for multidisciplinary Program Project

Item	Action Taken or to be Taken
Bionutrition	Grant (P01) applications in nutrition and basic biology, to focus on the role of nutrition in the initiation, promotion, and progression of cancer. The goal is to develop dietary interventions for cancer prevention, particularly breast cancer, prostate cancer, and cancer in women and minorities. Currently ongoing clinical trials are examining how the modification of dietary fat intake may affect cancer risk.
Proton Therapy	
3. The House in its report 103-553, page 46, stated, "Over the past four years, at the Committee's initiative, NCI has provided funds for the planning, design and construction of a competitively selected and peer reviewed proton therapy research center. The Committee is pleased that the project is on schedule and urges continuation of this initiative."	A specialized Proton Beam Therapy Facility, the Northeast Proton Beam Therapy Center at the Massachusetts General Hospital in Boston has received NCI funding to initiate research into this promising treatment technology. The NCI will continue to support the development of proton beam research.
Skin Cancer	
4. The House in its report 103-553, page 46, stated, "The Committee is concerned about the rapid increase in the incidence of skin cancer, especially malignant melanoma. Since 1980, the incidence of malignant melanoma, the most deadly form of skin cancer, has increased over 65 percent. The Committee urges the Institute to make melanoma research one of its priorities and to be prepared to testify before this Committee next year on its efforts to combat this deadly form of cancer."	The NCI continues to support melanoma research aimed at detection, treatment, and prevention, including the development of vaccines. A melanoma-specific antigen MAGE-1, which although specific may be quite rarely expressed on melanoma cells, will enter clinical trials in the near future. A newly discovered melanoma antigen, MART-1, appears to be expressed even more frequently than MAGE-1, and a vaccine containing MART-1 will be ready for clinical testing by the end of FY 1995.

FY 1995 Senate Report

Prostate Cancer	Action Taken or to be Taken
1. The Senate in its report 103-318, page 71, stated, "The Committee is concerned that the incidence continues to increase and urges the maintenance of a strong prostate cancer program at the Institute. Particular attention should be given to the very high rates of prostate cancer among African-American men. The Committee urges the NCI to collaborate with the urology program at the NIDDK on research geared toward the development of effective early detection techniques and innovative treatments for the disease."	The Prostate Cancer Prevention Trial (PCPT) is testing the ability of Finasteride (Proscar) to reduce the incidence of prostate cancer. Black men and men with a family history of prostate cancer are being aggressively recruited for this trial, which will also evaluate the benefit of annual prostate examinations and serial prostate-specific antigen (PSA) blood tests for detection. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) is a clinical trial designed to determine whether the number of deaths can be reduced through early detection of these cancers. In a large study of tumors that occur excessively in African Americans, dietary intake of micronutrients, fruits and vegetables, fat, meat and alcohol are being examined. Also, questionnaire analysis from the Health Professionals' Follow-Up Study suggests that fat consumption (especially red meat) is directly related to prostate cancer risk. Basic scientists continue exploring the molecular and cellular events associated with prostate cancer. Investigators are studying molecular genetic and cytogenetic alterations in prostate tumors, including specific genes uniquely expressed in these tumors. Studies of tumor heterogeneity are working to insure accurate diagnosis and prognosis. A clinical study with prostate specific antigen (PSA) in a vaccinia vector has recently begun. Basic research targeted at identification of tumor antigens has improved prospects for identification of antigens in prostate carcinomas. The NCI SPORE program (Specialized

Item	Action Taken or to be Taken
Prostate Cancer	Programs of Research Excellence), intended to accelerate translational research, now includes two prostate cancer SPOREs. To complement these SPOREs, NCI is initiating planning this year for Prostate Cancer Research Programs in traditional Cancer Centers. In addition, the NCI is co-funding three O'Brien Urological Research Centers with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). These three centers are specifically addressing prostate cancer. Finally, a number of new chemoprevention clinical trials are planned to accelerate applied research in prostate cancer prevention.
Psychosocial Support	
2. The Senate in its report 103-318, page 71, stated, "The Committee is greatly concerned that socioeconomically disadvantaged and cultural minority populations are most likely to have higher rates of cancer morbidity and mortality. Accordingly, the Committee expects the NCI to expand research on psychotherapeutic, psychosocial support, and community care services that are tailored for these vulnerable populations."	The increased emphasis on disease prevention and early detection has resulted in many persons learning of their increased risk of cancer through general medical risk assessments, results of routine screening procedures, or a diagnosis of cancer in a relative. Because risk notification contains diverse potential psychological impact and ethical implications, NCI-sponsored research is evaluating specific counseling interventions to increase compliance with recommended therapy in newly-diagnosed cancer patients. Research is also focussing on methods for increasing adherence to early detection programs in persons notified of high cancer risk. This initiative is also aimed at improving quality of life in these groups. NCI supports research for developing and testing techniques for measuring health-related quality

Item	Action Taken or to be Taken
Psychosocial Support	of life in cancer patients from culturally diverse backgrounds. Cancer clinical trials are now adding quality-of-life endpoints to traditional outcome measures.
Native Americans	
3. The Senate in its report 103-318, pages 71-72, stated, "Cancer is the leading cause of death for Alaska Native women, the second leading cause of death for American Indian women, and the third leading cause of death in American Indian and Alaska Native men. The Committee urges NCI to continue to expand its efforts targeted toward these groups. The Committee also wishes to be assured that the citizens of the State of Hawaii have ready access to state-of-the-art cancer care through the opportunity to participate in federally supported clinical trial groups."	The Native American Women's Cancer Initiative has identified numerous barriers that interfere with cancer prevention and control efforts among American Indian and Alaska Native (AIAN) women. Furthermore, it has been determined that the types and impact of such barriers vary among AIAN communities in different regions of the country. Research is focussing on identifying barriers to culturally appropriate quality cancer control services and reducing cancer risk behaviors in AIAN women. The NCI works with the Indian Health Service to address differentials in cancer incidence, mortality, and survival between minority populations and the general population. The NCI is planning another cancer prevention and control initiative which will include American Indians, Alaska Natives, Native Hawaiians, and American Samoans. The initiative, called the Native American Leadership Initiative on Cancer (NALIC) is intended to stimulate the participation of AIAN community leaders in cancer prevention and control outreach activities. Additionally, the NCI currently has research underway to assess the needs and to identify barriers to cancer prevention and control in communities or organizations within native Pacific populations. This initiative includes testing ways to adapt existing intervention methods to make them more culturally

Item	Action Taken or to be Taken
Native Americans	sensitive to Native Pacific populations. Finally, the NCI collaborates with the University of Hawaii, its affiliated hospital systems, and the Tripler Army Medical Center to encourage participation in clinical trials.
Bionutrition	
4. The Senate in its report 103-318, page 72, stated, "The Committee is concerned...because the National Cancer Institute may be terminating its investment in clinical nutrition research units. The Committee believes that CNRU's and similar programs are essential to link basic and clinical science. The Committee also encourages the national Cancer Institute to further explore the role of nutrition and women's health including breast cancer.	The NCI continues its commitment to the diet and cancer research program begun in 1982. Research focusses on cancer causation in addition to dietary interventions for cancer prevention and control. Research funding is awarded to projects of the highest scientific merit, as judged by peer review, which address those goals. For example, ongoing studies of heterocyclic amines (HAAs) have shown that these procarcinogens are produced in meats cooked at high temperatures, a practice common in our diet. Other cancer studies, such as the Long Island Breast Cancer Study Project, include the assessment of dietary factors in breast cancer risk. Another large case-control study includes the examination of adolescent dietary patterns as they relate to breast cancer risk in young women. Numerous multi-ethnic minority studies are examining ethnic diversity in diets and the risk of breast cancer. In addition, the role of diet is being analyzed in a large study of tumors that occur excessively in African Americans, including the intake of micronutrients, fruits and vegetables, fat, meat, and alcohol. Analysis suggests a link between fat intake (especially red meat) and advanced prostate cancer risk. A large occupational cancer study in agricultural workers includes

Item	Action Taken or to be Taken
Bionutrition	analysis of cancer risks associated with diet and various cooking practices. In addition, NCI's Interactive Research Project Grants support interdisciplinary collaborative research to address the complex questions about quantifying the role of diet in cancer prevention. The NCI has also issued a request for multidisciplinary Program Project Grant (P01) applications in nutrition and basic biology, to focus on the role of nutrition in the initiation, promotion, and progression of cancer. The goal is to develop dietary interventions for cancer prevention, particularly breast cancer, prostate cancer, and cancer in women and minorities. Currently ongoing clinical trials are examining how the modification of dietary fat intake may affect cancer risk. One study is examining the relation between diet and major cancers (breast, large bowel, and prostate) in a population of early-to late-middle aged men and women. Another study is intended to determine whether a low-fat, high-fiber, and high-fruit and vegetable dietary pattern will decrease the recurrence rate of adenomatous polyps of the large bowel. Finally, the NCI continues support for the National 5-A-DAY Program, designed to encourage Americans to eat five or more servings of fruits and vegetables every day.
Diethylstilbestrol (DES)	
5. The Senate in its report 103-318, page 72, stated, "The Committee is aware of reports that there may be third generation DES health effects--health problems among the sons and daughters of	A feasibility study has just been completed to determine the feasibility of studying 3rd generation DES health effects. The NCI will award a contract to complete a study involving more

Item Diethylstilbestrol (DES)	Action Taken or to be Taken
DES daughters and sons--and urges that this issue be studied."	formal assessment, including physical examinations of 3rd generation DES offspring, and assessment of disease outcomes. The effect of DES exposure during pregnancy continues to be studied, with cohorts of 6,000 mothers, 6,000 daughters and 3,000 sons who are under active follow-up to measure cancer incidence and mortality. Additionally, NCI is sponsoring an initiative to develop, implement, and evaluate health education programs to inform DES-exposed mothers and offspring about the risks associated with DES exposure. This initiative includes identification of strategies for early detection, diagnosis, and treatment. A national education program is now being conducted to test a regional breast cancer screening program for women exposed to DES.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation...	Section 301	42USC241	Indefinite		Indefinite	
National Cancer				--> $1,879,363,000		--> $1,954,348,000
Institute........	Title IV, Part A	42USC285	Indefinite		Indefinite	
	(Sec 408 (a)(1)(A))		Indefinite	(1,686,980,000)	Indefinite	(1,732,078,000)
	(Sec 408 (a)(1)(B))		Indefinite	(192,383,000)	Indefinite	(222,270,000)
National Research Service Awards..	Section 487(d)	42USC288	Such sums as necessary	38,541,000	Such sums as necessary	39,659,000
Total, Budget Authority........				1,917,904,000		1,994,007,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1987	$1,158,089,000[2]	$1,346,751,000[2]	$1,397,250,000[2]	$1,402,837,000
1988..........	1,302,823,000	1,448,411,000[3]	1,527,054,000	1,469,327,000
1989..........	1,468,256,000[4]	1,593,536,000	1,591,036,000	1,571,879,000
1990..........	1,494,741,000[5]	1,652,666,000	1,668,473,000	1,657,161,000[6]
1990 Sequester				-22,829,000
1991..........	1,694,059,000	1,749,392,000[7]	1,747,462,000	1,714,784,000[8]
1991 Sequester				-22,000
1992..........	1,810,230,000	1,830,509,000	2,010,230,000	1,962,587,000[9]
1993..........	2,010,439,000	1,998,616,000	2,010,439,000	1,981,351,000[10]
1994..........	2,142,122,000	2,082,267,000	2,082,267,000	2,076,382,000
1995[11]..........	1,967,709,000	1,917,929,000	1,917,929,000	1,916,920,000[12]
1996[11]..........	1,994,007,000			

[1] Reflects enacted supplementals, rescissions and reappropriations.

[2] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $61,674,000 for NCI.

[3] Excludes funding for AIDS research. Proposed to be at the Secretary's level.

[4] Excludes funds for AIDS research and education [$125,280,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[5] The 1990 request excludes funds for the National HIV program [$151,332,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[6] Excludes enacted administrative reduction of $6,839,000.

[7] Excludes $35,793,000 for NRSA training programs not considered.

[8] Excludes enacted administrative reductions of $42,568,000 and $8,972,000.

[9] Excludes enacted administrative reductions of $22,255,000, $482,000, and $3,954,000.

[10] Excludes enacted administrative reductions of $16,060,000; $9,933,000; and $139,000.

[11] Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

[12] Excludes enacted administrative reductions of $1,482,000, $116,000, and $901,000.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity

(dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Research:												
Cancer causation.......	724	$490,640	715	$492,322	620	$511,158	600	$528,818	590	$546,742	-10	+$17,924
Detection and diagnosis research............	206	121,299	202	134,339	154	134,199	126	133,170	121	135,449	-5	+2,279
Treatment research.....	943	549,954	937	550,568	860	541,502	833	530,655	823	551,174	-10	+20,519
Cancer biology.........	462	286,996	459	301,111	476	285,410	476	296,423	476	305,974	---	+9,551
Subtotal, research.....	2335	1,448,889	2313	1,478,340	2109	1,472,269	2034	1,489,066	2009	1,539,339	-25	+50,273
Resource Development:												
Cancer centers support.	14	141,468	18	143,647	13	156,897	12	155,873	12	155,915	---	+42
Research manpower development..........	40	64,360	35	62,899	26	64,086	24	65,012	23	67,827	-1	+2,815
Construction...........	4	12,273	4	7,846	3	16,822	3	8,325	3	3,331	0	-4,994
Subtotal, resource development..........	58	218,101	57	214,392	42	237,805	38	229,210	37	227,073	-1	-2,137
Cancer prevention and control..........	225	114,913	231	112,579	231	153,855	243	199,628	243	227,595	0	+27,967
Subtotal, obligations..	2618	1,781,903	2601	1,805,311	2382	1,863,929	2315	1,917,904	2289	1,994,007	-26	+76,103
Unobligated balance lapsing..............		16		80		164		0		0		---
Total, budget authority	2618	1,781,919	2601	1,805,391	2382	1,864,093	2315	1,917,904	2289	1,994,007	-26	+76,103

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

Justification

National Cancer Institute

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2382	$1,864,093,000	2315	$1,917,904,000	2289	$1,994,007,000	-26	+$76,103,000

General Statement

This document provides justification for the FY 1996 non-AIDS activities of the National Cancer Institute (NCI). Justification of the NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

NCI's mission is to conduct scientific studies and generate the knowledge that we as a nation need to reduce death and suffering from cancer. To achieve this goal, the Institute relies on its foundation stones of basic research, clinical trials and a nationwide network of cancer centers. NCI provides support for peer reviewed research across the country in many biomedical research institutions and medical centers. As a result of the investment in the NCI we have new theoretical insights and exciting approaches to the treatment of cancer.

The urgency of NCI's mission is clear: this year in the United States 1,252,000 cancer cases will be diagnosed and about 547,000 Americans will die of this disease. Breast cancer will strike 183,000 Americans this year, prostate cancer 244,000, and colorectal cancer approximately 138,000 Americans. Lung cancer, rare at the turn of the century, will afflict approximately 170,000 Americans this year. Recent statistics show about a 5 percent decrease between 1989-1992 in deaths due to breast cancer in American women. For white women the decrease is seen in virtually every age group. For white women ages 30 to 39, the decline has been almost 9 percent. This unfortunately is not true for African American women. This improvement appears to result from adjuvant therapy, breast cancer awareness, and screening, and affirms the need for a balanced research program and a redoubled effort to see that all Americans benefit from NCI programs. Such highly prevalent cancers are high NCI research priorities.

We all take heart from the increasing number of cancer survivors, some 8 million strong who themselves have joined together to teach us the lessons they have learned from their individual struggles with cancer. They have brought increased attention to pain control and rehabilitation. The search continues for the minimum treatment consistent with the best cure. Scientists are focusing on issues intrinsic to being a cancer survivor and looking at therapies with an eye to quality of life during and after treatment.

Actually what we call "cancer" is a family of more than 200 diseases, characterized by uncontrolled and destructive cell growth, which can afflict virtually any part of the human body. Some cancers may be inherited but most are the result of injuries to genes in cells caused by bacteria, viruses, lifestyle--such as diet or tobacco use--or environmental factors. Cancer develops through a multi-step process, involving an intricate series of events at the molecular level. Usually there is an initial event that begins the process, followed by other events which promote the development of a tumor. Stimulation of certain cancer-associated genes or a loss of tumor suppressor genes, are the events that lead to malignant changes in cells.

NCI-supported scientists have painstakingly uncovered and described many of these critical events. Studies comparing cancer and normal cells have helped to find significant regulatory events involved in the development of cancer. Many of the techniques developed to conduct such research gave rise to the field of biotechnology and innovations such as gene therapy.

Cancer is usually curable when it remains confined to the original site, but once metastasis occurs and cancer spreads, it is much harder to control or cure. NCI studies have helped to define the process of tissue breakdown that allows the cells to travel and have identified ways to stop metastasis. Several compounds that can inhibit the spread of cancer cells are now in early clinical trials.

In some cases considerable time elapses from the initiating event, for example, tobacco use, radiation, including sunlight or certain viruses, and the onset of a related cancer. Other factors then come into play and are spoken of as cancer promoters speeding the development of a tumor. In melanoma, for instance, sunlight is both an initiator and a promoter. Although the long lag, sometimes measured in decades, has served to obscure the relationship between the initial instigation and the resultant tumor, it also allows for intervention and prevention.

There has been an explosion of information about genes involved in cancer. Genes associated with some forms of breast cancer, kidney cancer, colon cancer, prostate cancer, and melanoma have been recently identified. Each new genetic discovery points to possible new diagnostic tests, preventive approaches and therapies. A number of projects in collaboration with the NIH Human Genome Project are in place.

Today, there are over 70 gene therapy protocols, with many different approaches. Gene therapy has been used to treat melanoma, kidney cancer, small cell and non-small cell lung cancer, ovarian and breast cancer, neuroblastomas, glioblastomas, and various lymphomas and leukemias as well as immune disorders and cystic fibrosis. Recent applications have been in cardiovascular disease.

Progress has been made in discovering some of the underlying molecular events in breast cancer. BRCA-1 located on chromosome 17, is a gene linked to breast cancer susceptibility as well as ovarian, colon and possibly, prostate cancer. There are early reports by NCI-supported scientists of a second familial breast cancer gene BRCA-2 on chromosome 13. While these genes account for only a small number of the total breast cancer cases in the United States, they provide scientists with valuable information. BRCA-1, so elusive and long sought by many research teams, still frustrates researchers as it is an extremely complex gene and early efforts to create a screening blood test have been disappointing.

An increased risk of breast cancer has been observed in families with other inherited syndromes, including the Li-Fraumeni syndrome, characterized by soft-tissue sarcoma, breast cancer and leukemia, and linked to mutations in the p53 tumor suppressor gene on chromosome 17, and ataxia-telangiectasia, which is linked to the AT gene on chromosome 11. In some types of inherited cancers, the genes involved may also be involved in the more common sporadic forms of the disease as well. However, genetic endowment is not synonymous with destiny as even with BRCA-1 some women escape breast cancer and this is being carefully studied as well.

Colon cancer strikes an estimated 100,000 Americans per year and kills about 48,000. NCI-supported scientists have described genes associated with inherited forms of colon cancer. Mutations in two genes, hMSH2 and hMLH1, are associated with a high percentage of hereditary non-polyposis colorectal cancer (HNPCC) cases. Such mutations account for roughly 15 percent of overall colon cancer cases and are also linked to a number of other cancers occurring within the affected families--notably endometrial, stomach, bladder, ovarian, and possibly, breast cancers. Scientists can now identify members of HNPCC families with increased risk of disease.

Although only the beginning of an answer, each new genetic discovery points to the possibility of new preventive approaches and therapies to prevent the growth and spread of cancer. However, new blood or urine tests that screen for missing or altered genes are in use or in rapid development for breast cancer, prostate cancer, colon cancer, kidney cancer, and other tumors. Genetic screening tests will allow us to alert those at risk, find cancers easily, and allow us to test prevention and treatment regimens.

NCI supports cancer research through a number of approaches. Cancer causation research addresses the reasons that cancer develops and looks at the effect of many environmental factors and occupational hazards including radiation, organic solvents, chemicals, pesticides, insecticides, and viruses. Recent NCI-supported studies have shown that exposure to Helicobacter pylori bacterial infection is associated with ulcers and in some cases with stomach cancer and a form of lymphoma.

NCI has a number of projects that respond directly to public concerns in the arena of occupational carcinogenesis. One such study is the Long Island Breast Cancer Study Project (LIBCSP). Others include the Northeast/Mid-Atlantic Study, and the Agricultural Health Study and its parallel study, the Migrant and Seasonal Farm Workers Feasibility Study. Sophisticated epidemiological methods and new molecular analyses will be used where appropriate to better understand the interactions between inherited genetic patterns and environmental exposures.

Supported by NCI and the National Institute of Environmental Health Sciences (NIEHS), the LIBCSP will use epidemiologic methods to examine a wide variety of environmental factors, including exposures to pesticides and other organochlorine toxins, contaminated drinking water, indoor air pollution, aircraft and auto emissions, electromagnetic fields, hazardous waste and municipal waste. Dietary factors, radiation, estrogen exposures, and occupational exposures are also being assessed. The same agencies support the Northeast/Mid-Atlantic Study, focused on breast cancer and the environment which encompasses an area that includes the District of Columbia and nine states from Maryland to New England.

NCI, NIEHS and the Environmental Protection Agency (EPA), support the Agricultural Health Study of over 100,000 farmers and their families to evaluate cancer and other disease risks associated with various agricultural exposures such as pesticides, herbicides, fertilizers, viruses, UV-light, chemical solvents and engine exhausts. A study of migratory farm workers is associated with this study.

The ability to diagnose cancer and to assess treatment success is very important. There is a constant search for better ways to image and diagnose cancer with an emphasis on new high technology methods such as magnetic resonance imaging, computer-assisted radiology, ultrasound, and positron emission tomography. NCI has signed a Memorandum of Understanding with the National Aeronautics and Space Administration to exchange information on a variety of subjects including the effects of radiation and to tap space age technology for new cancer imaging methods.

NCI is evaluating many new screening tests including PSA for the diagnosis of prostate cancer and CA-125 for ovarian cancer in its Prostate, Lung, Colorectal and Ovarian (PLCO) screening clinical trial. Last year there were approximately 24,000 cases of ovarian cancer diagnosed and there is a urgent need for methods to detect it in the early stages of the disease. Prostate cancer also poses a diagnostic challenge as some tumors are slow growing and others very aggressive and tests are needed to differentiate between these tumors so that appropriate treatment steps can be taken.

NCI supports cancer drug discovery and development and conducts clinical studies on innovative approaches to cancer treatment. These include gene therapy, new tumor specific customized therapies, immunostimulants, cell growth factors, programmed cell death, and specially constructed antibodies which can carry a toxin or radiotherapy right to a cancer cell. NCI supported research is identifying the optimal use of the traditional modalities of surgery, radiotherapy, and chemotherapy singly and in combination. Cancer cells need their own blood supply to grow. Scientists are looking at new blood vessels as a measure of tumor aggressivity and seeking ways to stem this expansion to contain tumor growth. Strategy has shifted from a goal of killing cancer cells to an approach that keeps a cancer from progressing. New understandings of the immune system have allowed gene therapies, ways of strengthening the immune system and the development of cancer vaccines.

NCI-supported scientists are developing and testing vaccines against cancer. This is an area of research that is built on an understanding of the immune system and cancer cell biology resulting from basic investigator-initiated research. Currently vaccines are being tested in melanoma, breast and prostate, and gastrointestinal cancers.

NCI has pioneered the screening of agents of all sorts that might have potential anticancer activity. New and improved cell screens test chemicals and natural products for activity. Candidate agents are submitted not only from NCI searches, but from universities, pharmaceutical companies and private individuals. This intensifies and accelerates the arduous search for agents to be developed as cancer agents. A number of new drugs have been developed by NCI or with its support. Taxol, developed in large part by NCI, has been effective against advanced breast and ovarian cancers, and is currently in clinical trials for other cancers. A new semi-synthetic version of taxol developed not from the bark of endangered Pacific Yew tree, but rather from needles and twigs of a related commonly available shrub has just been approved by the Food and Drug Administration.

One of the most important new insights about cancer is that many types of cancer are preventable. Experts estimate that as many as 70 percent of all cancers are related to lifestyle choices such as diet or smoking. In 1982 NCI began a diet and cancer research program. Many foods, such as root vegetables, garlic, and citrus fruit were studied to identify the compounds that may help prevent cancer. In 1991 NCI announced, in collaboration with the food industry, the 5 A Day for Better Health Program to encourage the eating of more fruits and vegetables. In 1991, the Women's Health Trial began a minority group feasibility study to develop methods for achieving dietary change. This study was a prelude to the NIH Women's Health Initiative, the largest community-based clinical prevention and intervention trial ever conducted in the United States. NCI is a full participant in the NIH study, which focuses on methods to prevent cancer, heart disease, and osteoporosis.

NCI works toward prevention of cancer in many ways. Studies of the long progression of carcinogenesis have given rise to pharmacologic, nutritional, chemopreventive, and endocrinologic agents to inhibit, delay, or reverse the process. In some cases, older agents are tested as preventive agents. Tamoxifen has been used as an adjuvant treatment after surgery for breast cancer and now as a preventive agent in a large prevention clinical trial. Finasteride (Proscar), the agent used to alleviate benign prostatic hypertrophy, is now in a prostate cancer prevention clinical trial. Micronutrients such as vitamin A and vitamin D as well as plant phenolics, such as that found in green tea, have in many cases a positive effect on vulnerable cells and present promising avenues for clinical testing. For instance, the retinoids, related to vitamin A, have suppressed tumor growth in many types of cancer including skin, trachea, lung and mouth. Anti-inflammatory agents such as aspirin are also being studied. Some agents detoxify, some inhibit cell signaling. Some stimulate the immune system. It is vitally important to continue to test these approaches in clinical trials.

Because of the toll of smoking related cancers, NCI places a major emphasis on smoking prevention and cessation. NCI supports the American Stop Smoking Intervention Study (ASSIST), now in its second phase of active intervention. This study will reach 91 million Americans (20 million smokers) in 17 states. ASSIST represents a collaborative effort among the NCI, the American Cancer Society, state and local health departments, and other voluntary organizations to develop comprehensive tobacco control programs in 17 states across the United States.

Translating basic research discoveries into prevention strategies or new cancer treatments is a high priority for NCI. Laboratory advances are extremely important, but the challenge of translating them into prevention or treatment strategies is essential. Multidisciplinary teams at the NCI Specialized Programs of Research Excellence (SPORES) are working to rapidly develop new technologies for breast, prostate, lung, gastrointestinal and other cancers.

NCI's Surveillance, Epidemiology, and End Results (SEER) Program tracks cancer incidence, survival, and mortality for the United States. This information allows for examination of changing patterns, focusing on research and health care planning. The data are linked to information on cancer risk factors, prevention practices, and patterns of cancer care. Linkage of SEER's tumor registry data with Medicare files has produced reports on the cost of cancer care. SEER data show the effect of changes in medical practice, such as the use of PSA and subsequent diagnosis of prostate cancer, that influence cancer rates. Regional differences in incidence, survival, and mortality are being studied to reveal factors associated with reduction of cancer risk, such as the availability of prevention and control programs.

In addition to participation in the NIH Women's Health Initiative, NCI leads a trans-PHS working group to help coordinate breast cancer research throughout NIH. NCI also works with the DHHS Office of Women's Health to respond to the Breast Cancer Action Plan resulting from the Secretary's Conference on Breast Cancer.

NCI has a number of projects to encourage minority group members to learn to reduce cancer risk, to advance biomedical research careers and to provide for support for grantees who encourage minority group members to conduct cancer research. Support is also given to NCI-designated Cancer Centers to support minority cancer control efforts.

NCI's program of information dissemination has made the best information about cancer and cancer treatment easily available for the public, the patients and health care providers. Diffusion of research results and treatment advances to the public and to the professional and research communities is carried out through many professional meetings, workshops and via the Cancer Information Service (CIS) reached by its toll-free 1-800-4-CANCER telephone number, PDQ, CancerFAX, and the Journal of the National Cancer Institute.

The urgency of the cancer research mission is clear. Virtually every American family suffers from cancer. This is a time of considerable achievement and great promise in cancer research. The rapid discovery of genetic information raises other issues. Medical ethics and humane values demand that we develop appropriate counseling and outreach programs and provide the best medical opportunities for the individual, while at the same time, ensuring the privacy and confidentiality every citizen should expect.

The President's appropriation request of $1,994,007,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Cancer Institute during the last five years has been as follows:

	Amount	FTE
FY 1991	$1,550,777,000	2,438
FY 1992	1,781,919,000	2,618
FY 1993	1,805,391,000	2,601
FY 1994	1,864,093,000	2,382
FY 1995	1,917,904,000	2,315

Purpose and Method of Operation

The NCI supports cancer research through several major scientific approaches. Cancer causation research includes investigations into the fundamental causes of human cancer and includes studies in chemical and physical carcinogenesis, biological carcinogenesis, epidemiology, chemoprevention and nutritional research. Detection and diagnosis research includes studies designed to improve diagnostic accuracy, characterize the behavior of tumors and predict the course of disease, and to identify individuals at increased risks for particular cancers. Treatment research spans both preclinical and clinical research and includes innovative approaches to cancer treatment and the application of the traditional modalities of surgery, chemotherapy and radiation therapy. Cancer biology supports a wide spectrum of basic research and attempts to understand the details of how cancer grows and spreads. Cancer centers support provides core funding to cancer research centers located across the nation and supports a diversity of research approaches to the problem of cancer. Additionally, the newly established Specialized Programs of Research Excellence (SPOREs) provide funding to institutions to concentrate on laboratory and clinical approaches for major cancer sites. Research manpower development strives to ensure an adequate supply of cancer researchers. The Construction program permits the development of facilities required for cancer research. Cancer prevention and control research emphasizes the translation of research knowledge into health promotion and disease prevention activities for the benefit of the public.

Overall Budget Policy

The FY 1996 budget request for the NCI is $1,994,007,000, an increase of $76,103,000 over the FY 1995 comparable amount of $1,917,904,000.

The $1,994,007,000 for cancer research is an increase of 4.0% over 1995 and includes a targeted increase in breast cancer research. The FY 1996 NCI funding for breast cancer research will increase by $31,733,000 to a level of $344,733,000, which is an increase of 10.1% over the FY 1995 level. These funds will support implementation of the Breast Cancer Action Plan, in addition to research project grants and cancer control grants focussed on breast cancer. The Cancer Prevention & Control budget will increase to $227,595,000. Research Project Grants will remain a top priority of the Institute and this budget will provide for 860 competing awards, an increase of 103 grants over the comparable FY 1995 level. Funding for Cancer Centers will show no increase, while Research & Development Contracts will show a slight decrease (-1.7%), consistent with the NIH policy to fund additional Research Project Grants. In addition, a decrease associated with FTE reductions totalling $5,373,000 in Intramural research and Research Management and Support has been incorporated.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Research

1996 Authorizing Legislation - Section 301 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) and Section 408(a)(1)(B) of the National Cancer Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2109	$1,472,433,000	2034	$1,489,066,000	2009	$1,539,339,000	-25	+$50,273,000

PROGRAM ACTIVITY:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer causation.....	600	$528,818,000	590	$546,742,000	-10	+$17,924,000
Detection and diagnosis..........	126	133,170,000	121	135,449,000	-5	+2,279,000
Treatment research...	833	530,655,000	823	551,174,000	-10	+20,519,000
Cancer biology.......	476	296,423,000	476	305,974,000	0	+9,551,000
Total...............	2034	1,489,066,000	2009	1,539,339,000	-25	+50,273,000

MECHANISM:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	No	Amount	No.	Amount	No	Amount
Research projects....	3180	$920,184,000	3314	$959,085,000	134	+$38,901,000
Other research:						
Cooperative clinical research...........	232	77,233,000	232	79,594,000	0	+2,361,000
Minority biomedical research support...		3,099,000		3,316,000		+217,000
Other research related..............	141	5,569,000	141	5,569,000	0	0
Subtotal, other......	373	85,901,000	373	88,479,000	0	+2,578,000
Total, rsrch grants..	3553	1,006,085,000	3687	1,047,564,000	+134	+41,479,000
Research and development contracts....	165	128,384,000	154	126,231,000	-11	+-2,153,000
Intramural research..		279,576,000		287,277,000		+7,701,000
Research management and support........		73,966,000		75,117,000		+1,151,000
Cancer prevention and control.............	6	1,055,000	11	3,150,000	5	+2,095,000
Total, NCI..........		1,489,066,000		1,539,339,000		+50,273,000

Funding for the Research budget activity during the last five years has been:

	Amount	FTE
FY 1991..............	$1,289,384,000	2,191
FY 1992..............	1,448,905,000	2,335
FY 1993..............	1,478,420,000	2,313
FY 1994..............	1,472,433,000	2,109
FY 1995..............	1,489,066,000	2,034

CANCER CAUSATION RESEARCH

Cancer causation research includes carcinogenesis by chemical, physical and biological agents, and epidemiology, chemoprevention and nutrition. This multi-faceted research increases our understanding of the mechanisms of cancer causation and leads to new ways of preventing its development.

Rationale for the Budget Request

The FY 1996 request of $546,742,000 represents an increase of $17,924,000 over the FY 1995 estimate of $528,818,000. Efforts are supported through a comprehensive Extramural effort conducted by NCI grantees and contractors, as well as through an Intramural Research Program conducted by Federal scientists. The program plans for FY 1996 are as follows:

Heterocyclic Amines and Cancer - Intramural and Extramural Research

Ongoing studies of heterocyclic amines (HAAs) have shown that these procarcinogens are produced in meats cooked at high temperatures, a common practice in the Western diet. Metabolism studies in cynomolgus monkeys treated with HAA known as PhIP suggest that PhIP may prove to be carcinogenic in nonhuman primates. PhIP metabolites have also been identified in breast milk and their potential role in mammary carcinogenesis is being assessed. HAAs may also be associated with cardiac abnormalities. Studies have shown that cynomolgus monkeys chronically treated with the HAA known as IQ have elevated levels of DNA adducts in heart muscle. Research will continue to evaluate the carcinogenic potential of HAAs.

Women's Cancers - Intramural and Extramural Research

The Congressionally-mandated Long Island Breast Cancer Study Project, conducted jointly by NCI and NIEHS, is investigating the role of environmental factors in breast cancer risk in the New York counties of Nassau, Suffolk, and Schoharie and in Tolland county, Connecticut. The study will examine exposures to pesticides and other organochlorine toxins as well as contaminated drinking water, indoor air pollution, aircraft and auto emissions, electromagnetic fields, hazardous waste and municipal waste. Dietary factors, radiation, estrogen exposures and occupational exposures are also being assessed. A separate Congressionally mandated study jointly funded by NCI and NIEHS encompasses the District of Columbia and nine states from Maryland to New England. The Northeast/Mid-Atlantic Study will investigate various environmental factors and breast cancer risk, particularly pesticide exposures.

A study will evaluate breast cancer risk, breast disease and pesticide levels among a heavily exposed population in Triana, Alabama. A production plant discharged large quantities of DDT into a tributary of the Tennessee River in this area for several decades. Residents who consumed fish from the river were found to have accumulated body burdens of DDT above that of the general population. The study will use previously collected blood and adipose tissue samples from Triana's predominately African-American population.

A new study is looking at the long-term health effects of silicone breast implants and the risk for breast cancer and connective tissue disorders. The study will identify 12,000 women who had cosmetic breast surgery on average 10 years ago and compare them to the general population and another cohort of women who sought other types of plastic surgery.

A large population-based case-control study conducted in Atlanta, Georgia; Seattle, Washington; and five counties of New Jersey is examining oral contraceptives, alcohol consumption, adolescent dietary patterns, and other possible breast cancer risk factors in young women. Preliminary analyses suggest that oral contraceptive use increases breast cancer risk, particularly prior to age 35, and that women with a family history of breast cancer are the most susceptible. Further analysis will evaluate if these agents especially influence some subgroups or particular tumor types. Other research focusses on the use of menopausal estrogens and breast cancer risk, including a follow-up of participants in the Breast Cancer Detection Demonstration Project. Another study will examine breast cancer risk among 10,000 women who were treated for infertility.

In response to the NIH Revitalization Act of 1993, NCI has established the Inter-Agency Working Group on Breast and Gynecologic Cancer. The Group includes representation from throughout the NIH, the PHS, and other Government agencies. The Working Group has recently been designated by the Secretary, DHHS as the programmatic focal point for the coordination of activities and the dissemination of information under the National Breast Cancer Action Plan.

Genetic Epidemiology Studies - Intramural and Extramural Research

Studies are underway to investigate disease syndromes that predispose certain individuals to breast cancer such as Ataxia-Telangiectasia and Li-Fraumeni syndrome. Several large, population-based multidisciplinary studies are investigating the genetic epidemiology of breast cancer. These involve efforts to ascertain mutation frequencies of the *BRCA1* gene along with linkage studies to identify other breast cancer susceptibility genes such as the putative *BRCA2* gene. A request for applications (RFA) has been advertised soliciting extramural applications to collect data and biological specimens from patients with breast cancer family history. The goal is to provide a registry resource for interdisciplinary studies of genetic and environmental interactions in breast cancer etiology and to encourage translational research. NCI collaborates with the National Center for Human Genome Research to appropriately consider the ethical, social and legal issues that accompany scientific breakthroughs in this area.

Cancer in Minorities - Intramural and Extramural Research

A study in African-American women will evaluate genetic predisposition, reproductive and dietary factors and breast cancer risk. Another study is analyzing mutation patterns in the tumor suppressor gene *p53* in randomly selected cases of Japanese, Native American, Northern European, North American, Mid-Western Caucasian and African-American women and correlating them with exposures to environmental mutagens. A multi-ethnic, minority cohort study of diet and cancer will involve over 300,000 individuals from four ethnic groups: African-American, Japanese, Hispanic, and non-Hispanic whites. Ethnic diversity in diets, reproductive history, physical activity, and the risk of breast cancer, cardiovascular disease and stroke will be assessed. A study of approximately 50,000 African-American women will review obesity, cigarette smoking, physical activity, alcohol use, diet, exogenous estrogen use, reproductive factors and breast cancer risk.

Prostate Cancer - Intramural and Extramural Research

The role of diet is being analyzed in a large study of tumors that occur excessively in African-Americans. For prostate cancer, the intake of micronutrients, fruits and vegetables, fat, meat and alcohol are being examined. Another study is examining the role of heterocyclic amines in the etiology of prostate cancer. Analysis of a food-frequency questionnaire from the Health Professionals' Follow-Up Study suggests that fat consumption, especially red meat intake, is directly related to advanced prostate cancer risk.

NCI scientists have developed a transgenic mouse model for the multistep development of prostate cancer and have identified genetic regulatory elements which can target the expression of various genes in the prostatic epithelium. Intramural scientists have also refined and validated an animal model system for inducing prostate carcinogenesis in three month old Lobund-Wistar rats. This experimental animal model provides a new avenue for exploring the molecular and cellular events associated with prostate cancer development and may facilitate the identification of new agents to prevent and/or suppress prostate cancer incidence. In other studies, human prostatic epithelial cells infected with adenovirus or transfected with a plasmid containing SV40 virus genes were established in cell culture. The new cell line will provide an important tool for further studies on prostate carcinogenesis.

DES Research - Extramural Research

The effects of diethylstilbestrol (DES) exposure during pregnancy are under study, with cohorts of 6,000 mothers, 6,000 daughters and 3,000 sons who are under active follow-up for the development of cancer and other conditions. Continued follow-up of these cohorts will measure the incidence and mortality of cancer, particularly of the breast and reproductive system, and determine if the risk of hormonally-related tumors increase as exposed offspring age.

A New Species of *Helicobacter* - Intramural Research

NCI scientists have discovered a new species of *Helicobacter* in the bile channels of mice which causes active hepatitis and liver tumors in infected animals. This represents a new model to study the mechanisms of carcinogenesis by this bacteria, another species, *H. pylori*, of which is associated with gastric adenocarcinoma. NCI and NIDDK have jointly issued an RFA on "The Role of *Helicobacter* in Cancer" to promote research on *Helicobacter* and the etiology of gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma.

Environmental and Occupational Cancer - Intramural and Extramural Research

Because occupational exposures frequently exceed those found in the general environment, epidemiologic studies of workers provide a unique opportunity to evaluate the carcinogenic potential of chemical and physical agents. Areas of emphasis include exposures to pesticides, organic solvents, radiation, arsenic, silica and wood dusts. The collection of biological specimens also provides possible markers for environmental exposures, genetic susceptibility and mechanisms of carcinogenesis.

In collaboration with NIEHS and the EPA, the Agricultural Health Study of over 100,000 farmers and their families is underway to evaluate cancer and other disease risks associated with various agricultural exposures such as pesticides, herbicides, fertilizers, viruses, UV-light, chemical solvents and engine exhausts. An important component involves the cancer risk to women and children that may arise from indirect exposures to agricultural chemicals through ambient air drifts, handling contaminated clothing, and residues found on rugs, children's toys, and in drinking water. Also under study are cancer risks associated with diet and various cooking practices. A parallel project, the Migrant and Seasonal Farm Workers Feasibility Study, will evaluate the potential for conducting a study of cancer risks from pesticides and other agricultural exposures that may affect migrant and seasonal farm workers and their families. Special efforts are being made to include Hispanic and other minority farm workers in the study, by devising practical ways to surmount the difficulties associated with tracking migrant populations.

Environmental Radiation Exposure - Intramural and Extramural Research

Although high radiation doses have been shown to cause cancer, important questions remain about the effects of low-level exposures, along with host and environmental factors on radiation risks. Ongoing studies in radiation exposure are looking at the potential hazards associated with medical, occupational and environmental exposures and the value of exposure avoidance for cancer prevention. Areas of study include electromagnetic fields and the risk of childhood leukemia, microwave radiation from cellular phones and brain cancer, and indoor radon levels and lung cancer. Patients given diagnostic or therapeutic radiation are being followed to identify any potential cancer risk. Atomic bomb survivors continue to be evaluated as a key data source for radiation-related risk. Other populations under study include nuclear power plant workers, underground miners, Chernobyl clean-up workers and over 100,000 medical x-ray technologists who are being followed for low-dose effects and excess breast and thyroid cancer risk.

Neurofibromatosis - Intramural and Extramural Research

Clinical observations made from the study of rare disorders such as neurofibromatosis continue to provide the groundwork for basic investigations that, in turn, elucidate concepts with broad implications for normal and aberrant development at the levels of the individual cell and the whole person. The ability to identify and characterize the structure and function of cancer-related genes is fundamental to every discipline of basic and clinical cancer investigation. The study of certain familial cancers such as neurofibromatosis furthers our understanding of genomic imprinting, or gene expression. NCI's multidisciplinary collaborations throughout the NIH and the extramural community have led to expanded knowledge about the complications of neurofibromatosis 2 (NF2). Efforts to identify the NF2 gene and to describe the clinical characteristics of patients with this disorder will continue.

DETECTION AND DIAGNOSIS RESEARCH

Studies supported by the NCI are aimed at improving diagnostic accuracy; providing more informative tumor classification; developing better tools to monitor response to therapy; detecting cancer earlier both initially and at the time of recurrence; and developing tools to identify individuals at increased risk for particular cancers. Effective initial therapy depends on accuracy of diagnosis and precision of pathologic staging. Identification of subsets of patients who will benefit from particular therapeutic regimens depends on more complete characterization of tumors at the time of diagnosis. The clinician must be able to accurately measure the response to therapy and detect disease recurrence as early as possible. New tests to identify individuals at risk for specific cancers will allow more appropriate counseling of families and more targeted screening and monitoring programs. Rapid transfer of developments from basic research to clinical application continues to be encouraged, and specimen and data resources needed for this transfer are being supported.

Rationale for the Budget Request

The 1996 budget estimate of $135,449,000 represents an increase of $2,279,000 over the 1995 estimate of $133,170,000.

Breast Cancer - Intramural and Extramural Research

Cloning of familial breast cancer genes will permit identification of women at increased risk for developing breast cancer. The BRCA1 gene, located on chromosome 17, is estimated to underlie about half of early-onset familial breast cancer. The recently cloned BRCA1 gene will allow investigators to identify the range of alterations associated with familial breast cancer. This information can be used to develop diagnostic tests that will identify women in these families who are at increased risk. Investigators have also identified a region on chromosome 13 that contains a second familial breast cancer gene, BRCA2, and are attempting to identify and clone the relevant gene. Further study will be necessary to determine whether these genes play a role in sporadic breast cancers.

Over half of women newly diagnosed with breast cancer have no involvement of the axillary lymph nodes and are considered to have a good prognosis. However, approximately 30 percent of these patients will ultimately die of metastatic breast cancer. Markers are needed to identify those patients who are at high risk for recurrence and should be treated more aggressively, and sparing patients at low risk from being subjected to highly toxic therapies. Studies using large numbers of samples are required to determine which predictive markers can provide the information the clinician needs to determine the best treatment. To make such specimens available to the research community, the NCI provided funds to establish the Cooperative Breast Cancer Tissue Registry. The registry expects to make available specimens from about 20,000 breast cancer patients and to begin distributing tissue specimens early in 1995. FY 1996 funds will ensure continued tissue availability, so that promising markers can be evaluated in a timely manner.

A number of markers have been tested for their ability to improve prediction of recurrence and survival in node-negative patients. These include over-expression of the tumor suppressor gene, p53, increased proliferative activity, and amplification or overexpression of HER-2/neu. However, there have been conflicting results from studies of these markers that probably reflect use of different methodologies and patient populations. A number of other markers have also been studied and reported to correlate with outcome, including expression of TGF-beta-1, cathepsin D, and thymidylate synthetase. The NCI will hold a conference in early 1995 to discuss the efforts being made by various scientific organizations to evaluate the data on marker studies and to recommend how to use markers for patient management.

A retrospective study of HER-2/neu overexpression in node-positive patients has suggested that this marker can be used to predict which patients will benefit from more intensive chemotherapy. Patients treated with the highest dose whose tumors over-expressed HER-2/neu survived longer than patients whose tumors did not demonstrate overexpression of the gene. This finding needs to be verified in another, larger group of patients. Higher doses have become standard practice so that the ability of marker expression to identify a group of patients with improved outcome will have to be tested in the context of recent practice. Such studies are being supported by the NCI in response to an initiative to study clinical correlations in breast cancer. FY 1996 funds would be used to complete patient follow-up.

Sophisticated molecular biologic techniques are being used to find potentially important chromosomal alterations in breast tumors. Regions on chromosomes 8, 17, and 20 were each found to be amplified in about one-third of breast tumors. Investigators are examining the amplified regions to determine whether they contain genes whose overexpression provides a survival advantage to the tumor cells.

Ovarian Cancer - Extramural Research

There is a need for markers that can predict the course of disease in patients with ovarian cancer so treating physicians may choose the best treatment. Histopathological examination of ovarian tumor tissue cannot adequately define which tumors with apparent low malignant potential will progress or which tumors will respond to particular therapies. The genetic events in the development of ovarian tumors have not been well documented but intensive investigations are underway in this area. About 5-10 percent of ovarian cancer cases can be attributed to inherited cancer syndromes, including ovarian, breast-ovarian and Lynch syndrome in which family members may have ovarian, breast, colon or uterine cancer. The BRCA1 gene has been shown to be linked to development of ovarian cancer in a number of families that have been studied. The genes involved in Lynch syndrome have now been identified and their role in ovarian cancer must be studied. These and other molecular genetic studies of ovarian cancer will provide important knowledge applicable to both hereditary and non-hereditary ovarian cancer. FY 1996 funds would support critical studies to determine whether genes involved in hereditary forms of ovarian cancer play a role in sporadic cases as well.

Prostate Cancer - Extramural Research

A network of six research groups is studying molecular genetic and cytogenetic alterations in prostate tumors, including specific genes shown to be uniquely expressed in prostate tumors. Other studies are evaluating a variety of growth factors, growth factor receptors and other molecules involved in regulation of the cell cycle.

Prostate cancer often presents with small foci of cancer scattered throughout the prostate. It is not known whether the foci result from multiple initiation events or from an initial event with subsequent dissemination of cancerous cells throughout the prostate. This complicates interpretation of individual biopsy specimens. NCI-supported investigators are looking at genetic alterations in individual foci from the same patient using selective ultraviolet radiation fractionation (SURF), a novel technique allowing separate analyses of small numbers of cells from different regions of the tumor. Studies of tumor heterogeneity are needed to insure that accurate diagnosis and prognosis is achieved from a limited number of patient biopsies.

Progress in Other Important Malignancies - Extramural Research

Studies of the genetic alterations associated with a familial form of colorectal cancer, hereditary non-polyposis colon cancer (HNPCC), have defined a new mechanism of tumor pathogenesis. Mutations in two genes, hMSH2 and hMLH1, are associated with a high percentage of HNPCC cases. The genes encode enzymes involved in DNA repair, and mutations in these genes result in generalized genomic instability. This instability is characterized by amplifications and deletions of small repeated sequences scattered throughout the genome, resulting in disruption of normal functions. These alterations can serve as a marker for identifying members of HNPCC families with increased risk of disease. The role of these genes in sporadic cases of colon cancer is being evaluated, and recent evidence has suggested that genomic instability may play a significant role in tumors of other organs as well. Further study is needed to confirm these findings.

NCI-supported investigators have developed sensitive PCR-based techniques for the identification of genetic alterations in the DNA from cells shed into the stool. Examination of stool for particular alterations associated with colon cancer or with premalignant changes could potentially be used for early detection or for monitoring for disease recurrence.

A network of NCI-supported investigators is carrying out a prospective study to confirm findings from earlier studies on several markers that appear to be useful for diagnosis and prognosis in early stage bladder cancer. They will test the feasibility of monitoring patients by measuring the markers in exfoliated cells found in voided urine or in bladder washings to avoid more invasive procedures. The markers will be assessed for their ability to predict which early stage tumors will recur and which of those that recur will become invasive. FY 1996 funding will continue these studies.

Progress in clinical correlative research will result in more effective use of available therapies. By linking studies of changes in tumor cells (markers) to clinical trials, it is possible to test whether a marker can predict response to a particular therapeutic regimen. NCI-supported investigators are pursuing marker studies linked to trials of therapies for colon, breast, lung and a variety of childhood tumors. This approach to marker evaluation will contribute to improved outcome and may save some patients from morbidity associated with ineffective treatments. FY 1996 funds would assure that these efforts continue.

Human Specimen Resources Facilitate Cancer Research - Extramural Research

The direct evaluation of human tumors is a critical step in the translation to clinical application of observations made in model systems. An adequate supply of high quality tumor tissues, normal control tissues and other specimens must be available to the research community in order to verify the presence and importance of genetic alterations, proteins or other markers in human cancers. The NCI has developed a variety of resources to meet these needs. The Cooperative Human Tissue Network is designed to meet the needs of basic exploratory studies which do not require extensive clinical or outcome data. Additional tissue resources with clinical and outcome data associated with each specimen have been developed by the NCI for investigators attempting to establish clinical correlations. The Gynecologic Oncology Group Ovarian Tissue Bank contains several thousand ovarian tissue specimens. The Cooperative Breast Cancer Tissue Registry is discussed in the section on breast cancer. The NCI regularly re-evaluates the need for tissue resources to best meet the needs of investigators and to facilitate scientific breakthroughs. FY 1996 funding would be used to maintain these resources.

TREATMENT RESEARCH

Over the past few years, the scope of research aimed at improving the treatment of patients with cancer has expanded dramatically to include gene therapy, a broad array of innovative approaches to vaccine therapy and other new strategies designed to improve the immune system's ability to kill cancer cells. In addition, efforts to discover and develop new anti-cancer drugs and to advance the traditional modalities of cancer treatment are continuing. Innovative cancer therapies derive from advances in our understanding of the molecular processes underlying malignancy, which can only come from continued support of a strong basic research effort. The NCI sponsors preclinical and clinical treatment research in both the intramural programs and in cancer centers, universities, and in industry. The NCI's drug discovery and development effort exemplifies the close interactions between the intramural and extramural research programs, as new natural products from tropical rain forests, semi-arid regions, and marine sources are collected by extramural grantees and through contract mechanisms, extracts are prepared and screened in intramural and contract laboratories, and further preclinical development of promising leads, including toxicologic and pharmacologic testing and chemical modification, is performed in intramural laboratories; trials in humans are then conducted in both the intramural and extramural clinical programs. Other routes to drug discovery, including molecular screening and rational drug design based on structural knowledge of key cellular proteins, will similarly require a concerted effort utilizing the full expertise of both NCI intramural scientists and extramural scientists and clinicians.

Rationale for the Budget Request

The FY 1996 request for $551,174,000 represents an increase of $20,519,000 over the FY 1995 estimate of $530,655,000. Efforts are supported through an Intramural Research Program conducted by Federal scientists integrated with a comprehensive Extramural Research effort conducted by NCI grantees and contractors located in cancer centers, universities, and in industry. The program plans for FY 1996 are as follows:

Paclitaxel (Taxol) Development - Intramural and Extramural Research

Paclitaxel is an effective anti-cancer agent that binds to and stabilizes microtubules, interrupting the process of cell division. Its activity was initially demonstrated in women with previously treated refractory ovarian cancer, and it has now also been demonstrated to be a very effective agent in women with breast cancer, and in patients with non-small cell lung cancer, head and neck cancer, esophageal, endometrial, and germ cell tumors, as well as Kaposi's sarcoma in AIDS patients. Currently, clinical trials are underway evaluating the efficacy of different doses of paclitaxel in combination with other drugs that are effective in ovarian cancer and breast cancer. The combination of paclitaxel and cisplatin gave response rates superior to those obtained with standard cyclophosphamide and cisplatin in women with ovarian cancer, and this combination appears to be the new standard regimen in ovarian cancer. Phase III trials are underway to determine whether this combination offers improved survival. Similarly, recent results from an Italian trial suggest that the combination of paclitaxel and doxorubicin may be the most effective therapy for women with breast cancer. A Phase III trial of doxorubicin vs. paclitaxel vs. combination paclitaxel and doxorubicin in breast cancer patients is underway. In addition, the first trial of paclitaxel in the adjuvant setting in breast cancer is underway, comparing cyclophosphamide plus doxorubicin (CA) for four cycles with the same regimen followed by an equal number of cycles of paclitaxel at standard or high dose.

Cancer Vaccines - Intramural and Extramural Research

Cancer vaccines are designed to stimulate the body's immune system, specifically the cytotoxic T-cell component of the immune system, to recognize tumor-specific antigens present on the surface of the cancer cell and to destroy the cell. Effective cancer vaccines could play a role in treatment of patients with minimal body burdens of tumor, as in adjuvant therapy following an initial tumor resection in patients at high risk for recurrence, and could be a potential preventive strategy in patients at very high genetic risk of cancer. Although earlier research focused on use of crude tumor cell preparations containing many different proteins, some specific and many non-tumor-specific, recently research in this area has focused on the use of single tumor-specific proteins, or even small antigenic portions of larger proteins, presented to the body in a context designed to maximally stimulate the immune response. Current approaches include (1) incorporating the gene for the tumor antigen into the genome of a viral vector, such as the vaccinia vector used for smallpox vaccines, followed by a standard vaccination technique; (2) use of purified protein or some polypeptide portion of a whole protein along with an adjuvant; (3) in vitro priming of blood antigen-presenting cells with a polypeptide antigen followed by reintroduction of the primed cells into the body. The development of cancer vaccines is an example of an area of potential significant benefit to patients that would not be possible without a sound understanding of basic immunology and cancer cell biology derived from an untargeted basic research effort.

The carcinoembryonic antigen (CEA) incorporated into a vaccinia vector is currently under study in patients with breast, gastrointestinal and lung cancers. Preliminary results have shown no responses, although immunological assays have demonstrated CEA-specific cytololytic T-cell responses in some patients, an absolute prerequisite for clinical activity. No toxicity has been noted. A similar clinical study with prostate specific antigen (PSA) in a vaccinia vector has recently begun. A melanoma-specific antigen MAGE-1, which although specific may be quite rarely expressed on melanoma cells, will also enter clinical trials in the near future.

Because a majority of gastrointestinal adenocarcinomas, pancreatic cancer and many other types of solid tumors contain specifically mutated *ras* oncogene protein, this protein is also a focus for vaccine development. Similarly, the p53 tumor suppressor gene is mutated in a variety of tumor types. These mutated normal proteins are being developed as cancer vaccines, using the various vaccination strategies discussed above.

An elegant approach to the screening for new tumor-specific antigens has led to the discovery of a new melanoma antigen, MART-1, which appears to be expressed much more frequently in melanoma than is the MAGE-1 antigen discussed above. MART-1 was cloned by screening a protein expression library prepared from melanoma cells for the ability of the protein to be recognized by, and to activate, HLA-A2 tissue-type specific cytolytic T-cells, the type of T-cells responsible for the killing of melanoma cells. A vaccine containing MART-1 will be ready for clinical testing by the beginning of FY 1996.

Radioimmunotherapy: Monoclonal Antibody - Radioisotope Conjugates
Extramural Research

Receptors and surface antigens of malignant cells are logical targets for therapeutic intervention. Monoclonal antibodies to a variety of growth factor receptors and other types of surface antigens have been prepared and used as a delivery system for either toxins or radioisotopes capable of killing the targeted cell by either disruption of critical intracellular processes (toxins) or by damaging DNA by ionizing radiation (radioisotopes). Both immunotoxins and immunoradioconjugates have been tested in clinical trials against various types of solid tumors and malignant lymphomas. Recently, two groups have reported significant response rates in patients with refractory indolent lymphomas using an I-131 labeled monoclonal antibody targeting a B-cell surface antigen. This I-131 B-1 antibody will be tested further to determine whether strategies can be developed combining radioimmunotherapy with conventional cytotoxic therapy to convert indolent lymphoma from an essentially incurable disease to one that is potentially curable.

Molecular Characterization of NCI Cell Line Screen
Intramural & Extramural Research

The NCI's new anti-cancer drug discovery effort hinges on the screening of plant extracts obtained from tropical rain forests and semi-arid regions and from marine organisms collected from around the world. This is a carefully integrated effort conducted by both intramural and extramural scientists. Extracts are screened for cell killing ability in a panel of 60 different cancer cell lines representing the gamut of human solid tumor types. Promising compounds are further tested in intramural and contract laboratories for pharmacologic and toxicologic properties, prior to beginning Phase I clinical testing. To date, over 34,000 agents have been screened. This process is fully automated. The output for any given agent is a "fingerprint" of activity against each of 60 cell lines, and this pattern can be compared with the pattern of all other agents through a computer program named COMPARE. Over the past year, a concerted effort by both intramural and extramural scientists has led to the characterization of the expression of a variety of genes in each cell line, with the generation of gene-expression footprints similar to the drug activity footprints. The genes already characterized or currently being examined include *ras* - family oncogenes, p53 tumor suppressor gene, bcl-2 apoptosis-suppressing gene, MDR-1 and MRP multi-drug resistance genes, topoisomerase I and II, glutathione transferase, EGF-receptor and a number of other oncogenes, cell-cycle control genes, tumor suppressor genes or other genes responsible for maintenance of the malignant phenotype or response or resistance to chemotherapy agents. With this added information, a COMPARE analysis of the drugs previously screened and future drugs screened can be used to discover drugs with previously unsuspected molecular targets or patterns of activity against certain molecular phenotypes. We anticipate that this analysis will also lead to enhanced understanding of the factors responsible for drug sensitivity and resistance.

Advances in Gene Therapy - Intramural and Extramural Research

A variety of strategies for treating cancer with gene therapy are being explored, and several innovative clinical trials have already begun. The early clinical trials focused on enhancing the ability of immune cells to target and kill tumor cells. An innovative approach currently being explored in clinical trials in patients with brain tumors is the use of "suicide vectors" to transfer a gene directly to tumor cells. The gene is capable of activating an otherwise non-toxic drug to make it toxic specifically to the cells that harbor the foreign gene. A bacterial gene coding for thymidine kinase (TK) is transferred to the rapidly cycling glioblastoma cells by direct implantation of a retrovirus vector producing cell line. Subsequently, gancyclovir is given to the patient. The gancyclovir is activated by the TK gene, which results in the death of the cells that harbor this gene.

Another approach is the transfer of a multi-drug resistance gene to normal bone marrow stem cells to enhance the ability of the marrow to tolerate high doses of chemotherapy.

Advances in Diagnostic Imaging - Intramural and Extramural Research

Extramural research in the area of diagnostic imaging technology development is supported by the NCI through the Diagnostic Imaging Research Branch. The NCI supports research in the area of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), ultrasound and optical imaging, digital mammography and other digital imaging technologies and positron emission tomography (PET). A major focus has been on the development of improved methods for early detection of breast cancer, particularly in younger women with mammographically "dense" breasts that make detection of breast cancer with mammography difficult. The most promising technologies in this regard are digital mammography and breast MRI. Several new programs for technologic development and clinical evaluation of these two modalities have been initiated within the past year and are continuing, including a grants program in digital mammography that was jointly conceived and funded by NCI and NASA. This Program Announcement is to transfer technologies initially developed for space and military purposes to medical uses.

Breast MRI is capable of detecting breast cancers significantly smaller than those detectable with conventional mammography. A Request for Applications will be issued in early FY 1995 for the clinical evaluation of MRI in women with abnormal mammograms, aimed at determining the sensitivity and specificity of MRI in this setting. Future studies may focus on breast MRI as a screening tool in certain populations at high risk for breast cancer.

An intramural NCI laboratory has developed an electron spin resonance (ESR) imaging instrument capable of detecting and imaging free radicals. Stable free radicals can be given intravenously to allow very sensitive anatomic imaging. In addition, endogenous free radicals present in tumor cells or in injured areas, such as in the heart muscle following a myocardial infarction or other sites of damage or inflammation can be imaged with this ESR instrument. Further development of this technology should contribute to research in cancer and other diseases, and may provide improved general imaging methods.

CANCER BIOLOGY

Cancer biology supports a broad range of investigator-initiated basic research on the biological characteristics of tumor cells and the interactions of tumor cells with normal cells of the host. A major goal of cancer biology is to understand the nature of the genetic changes in cancer cells and how they result in the observed cellular growth properties. Another area of investigation is the interaction between a growing tumor and the specific and nonspecific elements of the host immune system. Research progress in these areas is necessary for improved strategies for cancer prevention, diagnosis and treatment.

Rationale for the Budget Request

The FY 1996 request of $305,974,000 represents an increase of $9,551,000 over the FY 1995 estimate of $296,423,000. Efforts are supported through an Intramural Research Program conducted by Federal scientists integrated with a comprehensive Extramural Research Program conducted by NCI grantees and contractors. The program plans for FY 1996 are as follows:

Tumor Immunology and Cancer Vaccines- Intramural and Extramural Research

Research on vaccines for non-viral cancers has accelerated within the past year. A number of important discoveries have been made and clinical trials of many vaccine candidates are under way. A major issue remains the identification of tumor antigens, particularly those recognized by T lymphocytes. In past years, the discovery of one or two new tumor antigens recognized by T cells has been a major accomplishment. With the help of methodological improvements, new antigens are now being reported monthly, particularly in malignant melanoma. Melanoma has been the proving ground for the complex technology required to identify such antigens. Progress made in this tumor type has led to initiation of at least two new candidate melanoma vaccines. The progress has also improved prospects for identification of relevant antigens in other tumors, including breast, colorectal, ovarian, lung, liver and prostate carcinomas.

Cytokines, which are secreted molecules that control cell-cell interactions, show great promise in cancer vaccines. Interleukin 12 (IL-12), a relatively newly discovered cytokine of particular interest, biases the immune system toward a cellular response, which is generally beneficial for tumor immunity. IL-12 has remarkable antitumor activity by itself, but its principal benefit comes in combination with other cytokines. It activates natural killer cells and promotes the development of killer T cells. It has already been shown to promote the effectiveness of a vaccine against the protozoan parasite Leishmania major. In one recent study in mice, co-injection of normal cells engineered to secrete IL-12, along with a mouse tumor cell line significantly suppressed the growth of the tumor cells and promoted the development of antitumor immunity.

Newer and potentially more powerful vaccine strategies are under development to complement those now in clinical trials. One new strategy for improving the strength of an immune response is the use of genetic immunization. Immunization is done with a gene that encodes the antigen. The gene is introduced into the patient or experimental animal in a form that can enter cells and begin directing the synthesis of a tumor antigen, providing continuous exposure to the antigen and ensuring that the antigen is properly presented to the immune system. A recent study documents that this technique is successful in immunizing mice against the tumor-associated antigen CEA.

Programmed Cell Death/Apoptosis in Immunology and Cancer
Extramural Research

One of the most exciting areas of research in immunology and cancer involves the internal pathways that tell cells when to die. These death pathways, known collectively as programmed cell death (PCD) or apoptosis, have been shown to be critical for shaping the mature immune system. It is theorized that they may be suppressed in cancer cells, contributing to increased growth and drug resistance of cancer cells. Advances in molecular and cellular biology methodologies have recently fueled a dramatic increase in our understanding of apoptosis at the basic science level.

Several cancer genes have now been shown to be important in apoptosis. The most unequivocal linkage between a putative cancer gene and the control of apoptosis has been demonstrated for a gene called bcl-2, a gene first identified as overexpressed in human B-cell lymphomas carrying the t(14;18) chromosomal translocation. The bcl-2 gene plays a critical role in the regulation of cell death in immune cells. In addition to bcl-2, myc (associated with Burkitt's lymphomas), p53 (the most commonly mutated of all the cancer genes and associated with as many as 50% of human cancers), ras (mutated in many human tumors), Rb (deleted in retinoblastomas), abl (associated with chronic myelogenous leukemia) have now been implicated in the process. The recognition that apoptosis can play an important role in both immunology and cancer will greatly broaden our understanding of all stages of the disease process and its treatment.

It has been shown that the cytokine network and the cellular signalling events elicited by cytokines in the triggering of apoptosis are critical for understanding how tumor cells evade apoptosis. Normal regulators of hematopoiesis control the abnormal growth of certain types of leukemic cells, bypassing genetic abnormalities that give rise to leukemia, and suppressing malignancy by inducing differentiation to mature, nondividing cells. We can now inject cytokines directly or increase their production in patients with nonmalignant and malignant hematological disease. Hematopoiesis represents the balance of responses of a cell to positive and negative regulators; thus, support will continue for research which furthers our understanding of how the network of cytokines interact.

Cytokines and Non-Hodgkin's Lymphoma - Intramural and Extramural Research

Recent progress has been made in understanding the effects of cytokines on the development and progression of non-Hodgkin's lymphoma (NHL). NHL is a particular threat to patients with B-cell immunodeficiencies. Research has now shown that these patients have high serum levels of IL-6. This is an important finding because IL-6 is a potent stimulator of dividing and immature B lymphocytes. The high levels of IL-6 probably drive lymphocytes toward continuous growth, predisposing to B-cell lymphoma development. Research is underway to develop a means of inhibiting the IL-6 effects in immunodeficient patients, with the goal of reducing their risk of developing NHL.

A recently discovered cytokine, IL-14, appears to have the potential to influence the clinical outcome of patients with NHL. IL-14 is secreted by lymphoma cells, and stimulates the continued growth of the cells that produce it. Scientists have recently cloned the IL-14 gene. With this information, a defective substitute gene was synthesized and inserted into lymphoma cells. This induced lymphoma cells to stop IL-14 production and eventually resulted in the death of these malignant cells.

Other cytokines change or restore functions of the immune system. Recent studies revealed that IL-12 could alter the immune response so that individuals survived a potentially lethal infection. Also, the addition of IL-12 to cultures of human lymphocytes, obtained from immunodeficient patients, restored immune function to the lymphocytes. These results suggest that IL-12 may be useful in restoring immune function in cancer patients whose immune systems have become deficient because of their disease.

Tumor Cell Regulation by the Extracellular Matrix - Intramural and Extramural Research

Through the efforts of basic cancer biology research, many advances have been made in identifying some of the aberrant genes and proteins responsible for the phenotype of the cancer cell. However, investigators have recently begun to realize the important contribution made by cells in the surrounding micro-environment because of their potent influence on the tumor cell. This micro-environment consists of a complex web of large structural proteins in an extracellular matrix arrangement (the ECM), a variety of cell types and various hormones and growth factors.

The ECM acts as a regulator of cell behavior, modulating the ability of tumor cells to proliferate, move, and invade out of their local environment. An early step in cancer's malignant progression includes production of enzymes, called proteases, that can break down the surrounding ECM. It has been demonstrated that the relative level of certain of these digestive enzymes correlates with aggressiveness of the tumor cells. Mice genetically manipulated to express high levels of one type of protease form tumors of the mammary glands at high incidence. At the same time the tumor cells, or other cells, produce inhibitors of the proteases which can block disintegration of the micro-environment. The simultaneous imposition of both positive and negative regulatory controls strongly influences the behavior of the tumor cells. Inhibitors of tissue proteases actually act as tumor suppressing agents, thus synthetic protease inhibitors are being tested for their ability to reduce the growth of human tumors transplanted into nude mice, and to prolong survival of the mice. This research area will have high priority for FY 1996 support. Efforts will be expanded to design new methods of potential delivery of such inhibitors in vivo, to potentially block cancer metastasis.

Cell Signalling Mechanisms via Structural Proteins - Extramural Research

The mystery of how a cell can read information through its surface membrane and transmit it all the way to the cell's nucleus is also being solved. It requires that the connecting molecular pieces of the internal signalling network in the cell be identified. Two aspects of this research will continue to be supported: finding the chemical mediators that represent transmission of the message, and locating the structural proteins that support the signal transduction pathway.

The Ras-Pathway - Extramural Research

Epidermal growth factor (EGF) is a powerful regulator of cell growth which interacts initially with a cell receptor. Many of the sequential components of the signalling pathway for EGF are known: the EGF receptor; a series of small proteins such as ras and raf1, chemical signals in normal cells which are mutated and found in oncogenic forms in tumor cells; and a series of kinases that enzymatically modify target proteins, including proteins within the nucleus called transcription factors. These transcription factors directly regulate the activities of genes whose products are pivotal to the cell's final response to EGF. In the last year, other intermediates in this pathway were found, resulting in further clarification of how these molecular components link in this signal transmission network. The newest information shows that binding of EGF to its receptor induces modifications to that receptor, permitting its association with other intermediate protein modulators, and culminating in the activation of ras. Activated ras stimulates the activity of raf1, probably through direct interaction of the two proteins; activated raf1 then initiates the further downstream events in the signal pathway. Raf1 is an especially important part of this system since it has been identified as a component of another pathway that serves to block ras signalling, suggesting that the cell must constantly sort through opposing signals that can result from "cellular crosstalk" between pathways. Defining the major components in this complicated system is critical, as any one of them could become the target for discrete cancer therapies.

Cellular Matrix Basis for Signalling - Intramural and Extramural Research

The complex transmission of cellular signals requires extraordinary precision in positioning of the components for accurate interaction. There is now evidence that this is accomplished by a putative association between

120

an organized system of insoluble protein fiber networks and all the necessary enzymes, signalling molecules, co-factors, and other chemical compounds to which they are tethered or to which they stick directly. Research into the function of the cell's solid state architecture represents a radical new direction for cancer biology. From exterior to the interior of the cell this network includes the outer membrane, attached to a cytoskeleton that extends to the nuclear membrane and a nuclear matrix that stretches through the nucleus and provides the framework for such activities as gene expression and mRNA processing.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Resource Development

1996 Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) of the National Cancer Act.
1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
42	$237,805,000	38	$229,210,000	37	$227,073,000	-1	-$2,137,000

PROGRAM ACTIVITY:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer centers support	12	$155,873,000	12	$155,915,000	0	+$42,000
Research Manpower development	24	65,012,000	23	67,827,000	-1	+2,815,000
Construction	3	8,325,000	3	3,331,000	0	-4,994,000
Total	38	229,210,000	37	227,073,000	-1	-2,137,000

MECHANISM:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	No	Amount	No.	Amount	No	Amount
Research centers:						
Basic Research	12	$23,444,000	12	$24,430,000	---	+$986,000
Clinical/ comprehensive	44	104,387,000	44	107,224,000	---	+2,837,000
Subtotal, centers	56	127,831,000	56	131,654,000	---	+3,823,000
SPORE grants	13	25,816,000	13	21,993,000	---	-3,823,000
Subtotal, centers & SPOREs	69	153,647,000	69	153,647,000	---	---
Other research:						
Research career program	191	14,386,000	197	15,242,000	+6	+856,000
Cancer education	73	7,904,000	78	8,662,000	+5	+758,000
Total, rsrch grants	333	175,937,000	344	177,551,000	+11	+1,614,000
Training:						
Individual	163	4,444,000	163	4,573,000	---	+129,000
Institutional	1225	34,097,000	1225	35,086,000	---	+989,000
Total, training	1388	38,541,000	1388	39,659,000	---	+1,118,000
Research management and support		6,732,000		6,863,000		+131,000
Construction		8,000,000		3,000,000		-5,000,000
Total, NCI		229,210,000		227,073,000		-2,137,000

Funding for the Resource Development budget activity during the last five years has been:

	Amount	FTE
FY 1991	$170,595,000	49
FY 1992	218,101,000	58
FY 1993	214,392,000	57
FY 1994	237,805,000	42
FY 1995	229,210,000	38

Resource Development

CANCER CENTERS SUPPORT

The overall Cancer Centers budget supports two distinct programs: the traditional cancer centers supported through the Cancer Centers Support Grant (CCSG or P30), and the Specialized Programs of Research Excellence (SPOREs) supported primarily through the P50 grant mechanism. Each program also has associated planning grants supported through the P20 mechanism.

Traditional Cancer Center Support Grants (P30s)

The Cancer Centers Program is comprised of a diverse set of organizations, each with its own unique set of research programs and its own strengths and attributes. Four types of Cancer Centers are currently supported by the Program: basic (12), clinical (15), comprehensive (26) and consortium (1). Up to two new clinical centers may be funded in FY 1995, bringing the total to 56 centers. The purpose of the CCSG is to support the infrastructure of a center within the traditional, usually departmentalized, setting of a university or research organization. Cancer Centers focus on creating an interactive research environment, allowing all cancer-interested investigators to convene, share ideas, explore innovative approaches to cancer and engage in collaborative research projects. Through this interactive, cross-disciplinary effort, Cancer Centers are expected to generate innovative approaches and important new discoveries. Of particular importance are those discoveries from the basic science laboratories and disciplines that can be translated into relevant clinical research which will ultimately impact on the incidence and mortality of the disease. Such interdisciplinary research is emphasized by the Cancer Centers Program, and emphasized in the review criteria in which the quality of individual Cancer Centers are evaluated by peers. Although the CCSG provides the stabilizing framework for Center operations and includes significant support for leadership and shared resources and facilities, the research capability of the center is defined by the research grants and contracts obtained from a wide variety of Federal, State and private sources The overall success of Cancer Centers is highly dependent upon the ability of scientists within the center to obtain their own research support.

The Cancer Centers Program also supports Cancer Center Planning Grants (P20s). These grants allow smaller institutions a means by which to develop over a period of three years a Cancer Center that will ultimately be capable of applying for a CCSG. The aim is to encourage the establishment of Cancer Centers in geographically under-represented areas of the country.

Specialized Programs of Research Excellence (SPOREs-P50s)

In 1992, the NCI initiated the SPORE program to accelerate translational research in the major cancer killers. Translational research applies basic laboratory findings to patients and populations, and conversely, applies clinical research findings to new laboratory studies that may lead to new hypothesis-driven clinical trials and interventions. To date, nine SPORE (P50) awards have been made, four in breast cancer, two each in prostate cancer and in lung cancer, and one in colorectal and pancreatic cancer. The prostate cancer SPORE at the Baylor College of Medicine is designated the

Matsunaga-Conte Prostate Cancer Research Center after Senator Sparky Matsunaga and Congressman Silvio Conte.

SPOREs focus on translational research on the human disease. The goal is to accelerate research advances that reduce incidence and mortality from these cancers, and improve survival and quality of life. Most of the SPORES are a component of existing NCI-designated cancer centers (P30 awardees) and are able to take advantage of the resources and scientific expertise made available by these P30 grants. The SPORE program maintains specialized research resources which include a human tissue procurement facility for investigative purposes. The SPORE also provides opportunities for career development in translational research, for both new and established investigators. This is expected to enlarge the cadre of investigators dedicated to translational research on human cancer. A special feature of the SPORE is the developmental research program. This provides a significant and flexible source of funds to rapidly test novel ideas, and to respond to new research opportunities in a timely manner.

Rationale for the Budget Request

The FY 1996 budget request of $155,915,000 represents an increase of $42,000 over the FY 1995 estimate of $155,873,000. The budget proposed for the traditional P30 program and its associated planning grants will allow for support of 56 to 58 Cancer Center Support Grants and approximately 18 planning grants. The P20 planning grant component of the program was begun in FY 1992 and recompeted in FY 1995 in order to increase the number of Cancer Centers to achieve a better geographic distribution. Fourteen institutions were awarded under the first initiative, and up to five more will be added in FY 1995. The planning grants will mature and compete for P30 Cancer Center Support Grants in FY 1995 to FY 1998. The requested budget will allow for continued support for approximately 18 planning grants still under development in FY 1996.

A relatively large number of grants will compete for CCSG support in FY 1996 including 11 competing renewals from active Cancer Centers and new grant applications from a number of institutions with current P20 planning grants. Limited funding to support growth in existing Cancer Centers as well as the funding for new meritorious applications will be achieved through conservative budget approaches, cost containment measures, and program turnover.

The NCI initiated a Request for Applications in FY 1994 for the development of breast cancer programs in Cancer Centers over a period of one to four years. The program was cosponsored by the National Institute of Environmental Health Sciences and the National Institute on Aging. Eighteen grants were awarded in FY 1994 with future year commitments, and another nine were awarded for one year. Similarly, in FY 1995, the Institute initiated a four-year program for planning for the initiation of Prostate Cancer Research Programs using a model similar to the one described for the Breast Cancer Research Program. Both of these programs will benefit the Cancer Centers' capability to build an interactive research capability in these research areas, and will augment and complement the breast and prostate SPORE program.

In 1996, the NCI will continue a prevention and control research capacity building pilot program initiated in 1994, which generated a significant amount of interest and activity. One planned activity is for a workshop in Cancer Prevention and Control for the benefit of investigators at the Cancer Centers working in this important area. The workshop will provide opportunities for sharing information on barriers and successes in establishing strong cancer prevention and control research programs at Cancer Centers and a forum for discussion of methods by which to succeed in securing competitive funding for research projects. It will contribute toward new collaborations in the field, and cement current collaborative relationships.

Cancer Centers have a high degree of interest in two other areas of the program and are taking advantage of opportunities to build on their prevention and control research programs. Support is provided to Centers with meritorious Cancer Prevention and Control research development plans in two areas: 1) pilot projects in prevention and control research to allow for the generation of preliminary data and subsequent application for competitive grants, and 2) support of new investigators in prevention and control research for up to four years where tenure track academic positions are available. The program will allow Cancer Centers to develop the critical mass of investigators and build a base of competitively funded research projects on which to establish a formal, collaborative, interactive research program, the hallmark of successful Cancer Centers.

The developmental fund category of the Cancer Center Support Grant (CCSG) includes support for pilot projects which provides Cancer Centers with an opportunity to explore new ideas and develop new projects to compete for independent funding through grants and contracts. This provides the NCI with a flexible instrument to target funds and specifically encourage projects focused on high priority areas. Within the budget request for FY 1996, continued emphasis will be placed on high priority areas of research, including breast, ovarian and cervical cancer, prostate cancers, AIDS-related malignancies, gene therapy, vaccine development, cancer in the elderly and environmental factors influencing cancer. In addition, Cancer prevention and control research will receive continued emphasis, attention and encouragement. This area of research is well suited to concentrate on cancer problems of minorities, Native Americans and the elderly; as well as quality-of-life issues including pain management, psychosocial variables and rehabilitation.

The FY 1996 budget request for Cancer Centers includes $21,993,000 specifically designated for SPOREs, a decrease of $3,823,000 below FY 1995. This will permit continuation of ten SPOREs and will permit new initiatives within existing SPOREs as well as testing new ideas through innovative pilot studies. It would also permit the funding of three new SPOREs, and would maintain programmatic interactions within the SPORE network. There are no plans to continue the SPORE feasibility program which utilized the P20 mechanism in previous fiscal years.

Cancer Centers Minority Enhancement Award (MEA)

Through the Cancer Center Minority Enhancement Awards (MEAs), the Institute seeks to expand minority involvement in cancer control research. Institutions with NCI-funded Comprehensive, Consortium, or Clinical Cancer Center support grants, capable of accessing large minority populations on a regular basis, may apply for an MEA. These competitively reviewed supplements to Cancer Center Support Grants provide funds for increased minority involvement in a variety of programs and activities. Four MEA's are ongoing at cancer centers in North Carolina, California, Arizona and Florida. Among the significant outcomes has been the successful generation of new R01 applications to continue support for studies begun under the MEA.

RESEARCH MANPOWER DEVELOPMENT

The Research Manpower Development programs support the training of scientists and clinicians in research areas focused on the discovery of new methods and procedures for the prevention, detection, diagnosis and treatment of cancer. These researchers will provide the human resources needed for cancer research efforts in the next 10 to 20 years. In addition, support is provided for cancer education programs which support a spectrum of short and long-term projects concentrated in the cancer research field.

Rationale for the Budget Request

The FY 1996 request of $67,827,000 represents an increase of $2,815,000 over the FY 1995 estimate of $65,012,000. The program plans for FY 1996 are as follows:

National Research Service Awards (NRSA)

The NRSA program provides the broad-based research training that is required to address the increasingly complex aspects of cancer research. For example, these grants facilitate interdepartmental training programs of a multidisciplinary nature that are necessary for preparing future cancer scientists. The requested FY 1996 budget supports 1,388 full-time training positions (FTTPs) for pre- and postdoctoral trainees funded through individual fellowships and institutional training grants.

Research Career Program ("K" Program)

The Research Career Program provides young investigators and clinicians with the support they require to make the transition to fully independent researchers. The program will focus on three major areas of training: physician scientists who can translate new basic research knowledge into clinical applications; scientists and clinicians who will be prepared for careers in cancer prevention and control research; and faculty development for minority clinicians. The requested budget will add six awards and will continue to provide support for the Clinical Investigator (K08), Physician Scientist (K11), Clinical Oncology Development (K12), Preventive Oncology (K07) and Minority Health Professional Training (K14) awards.

Cancer Education Program

The Cancer Education Grant Program supports a spectrum of short- and long-term education projects in the basic, behavioral and clinical disciplines aimed at a wide segment of target audiences. These groups include various health professional communities, college and high school students (especially minorities), and cancer patients and their families. The FY 1996 request will continue support at current levels for these programs. Emphasis will continue in breast cancer and multidisciplinary training in cancer prevention and control. As some programs terminate, they will be replaced with programs in new areas of need such as intensive education in the design and management of treatment and prevention clinical trials.

Minority Focussed Training/Development

The Minority Biomedical Research Support (MBRS) and Minority Access to Research Careers (MARC) programs are administered by the National Institutes of General Medical Sciences (NIGMS). The NCI provides support for NCI mission-related projects of the MBRS program. The MBRS program provides expanded opportunities for ethnic minorities to participate in biomedical research careers. During FY 1994, awards were made to individuals at MBRS-eligible institutions that are engaged in cancer-related activities. Similarly, the MARC program was established to help minority institutions train greater numbers of minority scientists and teachers for biomedical disciplines.

The broader goal of NCI's minority program is to provide support to minority scientists by providing increased opportunities for expanding their capabilities in cancer research, and to encourage more minority scientists to develop careers in cancer research. The program also seeks to promote manpower development targeted towards fields of specialization that are experiencing minority shortages. This approach includes specialized research training of minorities at NCI-supported centers, involvement of affected minority populations in the implementation of cancer prevention and intervention programs, and participation of minority patients in clinical trials and other treatment programs, especially at minority institutions and hospitals.

Through the NIH-wide Minority Investigator Supplement (MIS) program, NCI has expanded its support to minority individuals pursuing careers in the biomedical research sciences. The program includes supplements for minority high school students, minority undergraduate students, minority graduate research assistants and minority individuals in postdoctoral training.

CONSTRUCTION

One of the objectives of the Construction program is to provide minimal funds for the annual maintenance and repair of existing Federal facilities located principally at the Frederick Cancer Research and Development Center. Such repairs would include utility upgrades, roofing repairs, heating and air conditioning repair and maintenance. These are items similar to those that are funded through the NIH Buildings & Facilities account for facilities on the NIH campus. On occasion, the development of additional research facilities for a specific objective would require construction funds. Also, this program permits the NCI to partially meet the need for expanding cancer research at universities and medical centers throughout the nation. Grants are awarded to expand and upgrade basic research laboratories, clinical research facilities and research animal facilities.

Rationale for the Budget Request

The FY 1996 request of $3,331,000 represents a decrease of $4,994,000 from the FY 1995 estimate of $8,325,000. The program plans for FY 1996 are as follows:

The FY 1996 request includes $1,000,000 for the continuation of limited Federal participation (on a 50:50 basis) in the construction and upgrade of facilities at medical centers and universities throughout the nation for laboratory and clinical cancer research, with an emphasis on breast cancer. The balance of $2,000,000 is requested for repair and maintenance of facilities at the Frederick Cancer Research and Development Center, as well as other research facilities across the nation.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Cancer Prevention and Control

1996 Authorizing Legislation - Section 301 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) and Section 408 (a) (1) (B) of the National Cancer Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
231	$153,855,000	243	$199,628,000	243	$227,595,000	---	+$27,967,000

PROGRAM ACTIVITY:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer prevention and control........	243	$199,628,000	243	$227,595,000	---	+$27,967,000

MECHANISM:	FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
	No	Amount	No.	Amount	No	Amount
Research management and support........		$8,300,000		$8,475,000		+$175,000
Cancer prevention and control:						
Inhouse..............		27,151,000		31,296,000		+4,145,000
Grants...............		74,130,000		83,749,000		+9,619,000
Contracts............		90,047,000		104,075,000		+14,028,000
Total, NCI..........		199,628,000		227,595,000		+27,967,000

Funding for the Cancer Prevention and Control budget activity during the last five years has been:

	Amount	FTE
FY 1991.............	$90,798,000	198
FY 1992.............	114,913,000	225
FY 1993.............	112,579,000	231
FY 1994.............	153,855,000	231
FY 1995.............	199,628,000	243

CANCER PREVENTION AND CONTROL

The NCI's cancer prevention and control research encompasses a full spectrum of basic through applied research, prevention clinical trials, and cancer surveillance. The translation of knowledge gained through prevention and control research into applications through technology transfer and health promotion activities for the public is a major priority of the Institute.

Rationale for the Budget Request

The FY 1996 request of $227,595,000 represents an increase of $27,967,000 over the FY 1995 estimate of $199,628,000. This level reflects adherence to the legislated requirement included within the NIH Revitalization Act of 1993 that the funding level for Cancer Prevention and Control in FY 1996 represent at least 10% of the NCI appropriation. The program plans for FY 1996 are as follows:

CANCER PREVENTION RESEARCH

Chemoprevention Clinical Trials

The ultimate goal of chemoprevention is to inhibit, reverse or prevent carcinogenesis, a process that begins with cells of normal morphology and ends with invasive cancers. The development of specific natural or synthetic chemical agents and clinical testing of these agents are major priorities of the NCI's chemoprevention program. Currently, 17 Phase I and 45 Phase II and III trials are supported through the chemoprevention program, to assess a highly diverse group of biological and chemical agents that have demonstrated anticarcinogenic activity. A new clinical program for Phase II trials has been instituted as follow-up to animal model studies. NCI-sponsored projects are expected to accelerate activities in the initial stages of developing and strengthening the rationale for chemoprevention trials. A number of new clinical trials are planned to accelerate the applied research in breast and prostate cancer prevention. In addition, new chemopreventive agents will be entered into intermediate biomarker (Phase II) and cancer incidence reduction trials (Phase III).

Alterations in the expression or function of certain classes of genes are critical events in the development of cancer. The NCI has introduced an initiative to facilitate chemoprevention research involving agents that may effect gene expression and cellular growth. This initiative also encourages the development and implementation of short-term clinical trials that evaluate the modulation/function of genes and gene products by chemoprevention agents. Research grants in chemoprevention will support multiple projects directed toward a specific major chemoprevention objective requiring a broadly based and multidisciplinary approach.

Dietary Interventions

Diet and nutrient-dependent mechanisms in carcinogenesis and cancer prevention are important research priorities. An understanding of these mechanisms in the initiation, promotion, progression and prevention of cancer may contribute to the design of dietary intervention trials as well as the identification of novel dietary effectors for cancer prevention. NCI's Interactive Research Project Grants support interdisciplinary collaborative research to address the complex questions about quantifying the role of diet and dietary components in cancer prevention.

NCI has issued a request for grantees to submit multidisciplinary Program Project Grant (P01) applications in nutrition and basic biology for cancer prevention. Specifically encouraged are the application of the techniques of molecular biology and molecular genetics to address questions about the fundamental role of nutrition in the initiation, promotion, progression and prevention of cancer and the use of that knowledge to develop dietary interventions for the prevention of cancer, with a special emphasis on breast cancer, prostate cancer and cancer in women and minorities.

There has been much speculation about potential mechanisms by which modification of dietary fat intake may affect cancer risk, but relatively little research in this area. Available evidence has been judged strong enough to justify recommendations for reductions in dietary fat intake to reduce cancer risk; the effects of such dietary modification are under investigation in ongoing clinical trials.

The relationship of dietary factors and major cancers, with particular attention focused on dietary fat and breast cancer, is under investigation in an important large-scale prospective study involving 3.5 million members of the American Association of Retired Persons in the initial screening, with the final cohort comprising 350,000 women and men aged 50-69. The objective of this study is to examine prospectively the relation between diet and major cancers (especially those of the breast, large bowel, and prostate) in a population of early- to late-middle aged men and women in the United States. Another study underway is a multi-center, randomized, controlled dietary intervention trial to determine whether a low-fat, high-fiber, and high-fruit and vegetable dietary pattern will decrease the recurrence rate of adenomatous polyps of the large bowel (Polyp Prevention Trial).

CANCER CONTROL SCIENCE PROGRAM

The American Stop Smoking Intervention Study (ASSIST)

ASSIST is a collaborative effort between the NCI and the American Cancer Society (ACS), along with state and local health departments and other voluntary organizations to develop comprehensive tobacco control programs in 17 states. Its purpose is to demonstrate that the wide-spread, coordinated application of the best available strategies to prevent and control tobacco use will significantly accelerate the current downward trend in smoking and tobacco use. The five year intervention phase began in 1993 and continues through 1998 (Phase II). More than 3,000 community organizations have joined ASSIST coalitions in the 17 states.

Minority Leadership Initiatives

Reducing Cancer in minority and underserved populations is facilitated by the mobilization of professional and lay leaders in the community to address the specific cancer needs of that community as well as through coalition building among health-related, academic and community organizations. The NCI supports three such initiatives in an effort to address the cancer prevention and control needs of certain populations. These include: the National Black Leadership Initiative on Cancer, the

Hispanic Leadership Initiative on Cancer, and the Appalachia Leadership Initiative on Cancer. The NCI also plans to support a Native American Leadership Initiative on Cancer (NALIC) to stimulate the participation of Native American community leaders in cancer prevention and control outreach activities. The initiative will include American Indians, Alaska Natives, Native Hawaiians, and American Samoans.

The Historically Black Colleges and Universities Cancer Prevention Awareness Project

Through a contract mechanism to Historically Black Colleges and Universities (HBCU's), a project for the purpose of developing and disseminating educational program information about the steps that can be taken to control cancer or reduce cancer risk and mortality in the African American population is ongoing. Currently, NCI supports contracts awarded to Texas Southern University and Meharry Medical College.

American Indians and Alaska Natives

Cancer has become the leading cause of death for Alaskan Native women and the second leading cause of death among both Native American and Native Hawaiian women. The Native American Women's Cancer Initiative was developed in response to emerging cancer needs and issues of Native American women. Numerous barriers have been identified that interfere with cancer prevention and control efforts among indigenous women. In addition, the types and impact of such barriers vary among Native communities in different regions of the country. Research projects focus on identifying barriers to culturally appropriate quality cancer control services and reducing cancer risk behaviors in Native American women. NCI is working with the Indian Health Service to address differentials in cancer incidence, mortality and survival between minority populations and the general population.

Cancer Prevention and Control in Low-Income Patient Populations

The goal of an Intra-agency Agreement with the Health Resources and Services Administration (HRSA) is to reduce or eliminate the disproportionately high burden of cancer incidence and mortality among the low-income segments of the U.S. population. The objectives are: to increase the application of state-of-the-art cancer prevention, early detection and screening, and treatment in approximately 500 Community and Migrant Health Centers; to evaluate the implementation and effectiveness of these intervention protocols in hard-to-reach populations; and to implement and disseminate these protocols throughout the Community and Migrant Health Centers.

Education Efforts for Native Hawaiians and Samoans

NCI is encouraging developmental research of Native Pacific populations to assess their cancer prevention, early detection and treatment needs. Research is underway to assess the needs and to identify barriers to cancer prevention and control in communities or organizations within native Pacific populations. In addition, research studies to test ways in which existing intervention methods can be adapted as well as designing new methods that are culturally sensitive to Native Pacific populations are the focus of this initiative.

National 5-A-Day Program

The National 5-A-DAY Program, designed to encourage Americans to eat five or more servings of fruits and vegetables every day, represents a significant public/private partnership between NCI and the Produce for Better Health Foundation. NCI's role to educate and provide credible information plays an integral part in communicating the 5-A-DAY message. State health agencies, universities and cancer centers awarded research grants are evaluating the effect of 5-A-DAY activities in schools, workplaces and other community settings.

National DES Educational Program

Diethylstilbestrol (DES) is a synthetic estrogen used to prevent miscarriages from the 1940s through 1971. DES was found to be associated with an increased incidence of rare vaginal clear cell cancer in young women who had been DES exposed in utero. NCI is sponsoring an initiative to develop, implement and evaluate health education programs to inform DES exposed mothers, daughters, sons and the health professionals who care for them about risks associated with DES exposure. This initiative also involves identifying appropriate early detection, diagnosis and treatment strategies for DES-related malignancies and other conditions. A national education program is now being conducted to test a regional breast cancer screening program for women exposed to DES.

EARLY DETECTION AND COMMUNITY ONCOLOGY PROGRAM

Community Clinical Oncology Program

The Community Clinical Oncology Program (CCOP) links community cancer specialists, primary care physicians and other health care professionals to conduct both clinical treatment research and cancer prevention and control research studies. The current program involves 48 community programs in 27 States with over 315 hospitals and 2,900 physicians. Through the network's access to cured cancer patients, their families and other individuals at increased risk of developing cancer, NCI implements large-scale chemoprevention trials to study the effectiveness of various agents to prevent cancer. Examples include the Breast Cancer Prevention Trial (BCPT) with tamoxifen, and the Prostate Cancer Prevention Trial (PCPT) with finasteride.

The Minority-Based Community Clinical Oncology Program (MBCCOP) provides minority cancer patients with access to state-of-the-art cancer treatment and control technology. The MBCCOP includes ten programs with greater than fifty percent of new cancer patients from minority populations.

Breast Cancer Action Plan

The National Action Plan on Breast Cancer (NAPBC) includes initiatives that will make an important contribution to the advancement of breast cancer research, and to the type of information dissemination that will help to prevent the morbidity and mortality from the disease. Many of the projects are built upon NCI's ongoing research program. These include: information dissemination; establishment of comprehensive patient registries and materials bank; biomedical and behavioral research related to breast cancer etiology; improved access to clinical trials for women with breast cancer or women at high risk; and an educational plan to assist individuals carrying breast cancer susceptibility genes.

Breast Cancer Prevention Trial

The Breast Cancer Prevention Trial (BCPT) is underway in the CCOP clinical trials network. This trial is testing the ability of tamoxifen, an anti-estrogen medication currently used in post-surgical treatment of early stage breast cancer, to prevent the development of breast cancer in women at increased risk for developing the disease. Approximately 16,000 women at increased risk for breast cancer due to age, family history and personal history are being randomized to receive tamoxifen or a placebo for an initial period of five years. The study, which will last ten years, is being implemented in over 250 nucleus and sub-centers across the country and in Canada. Samples are being collected from the trial participants to analyze any inherent genetic factors that may contribute to the risk of developing breast cancer in this population.

Prostate Cancer Prevention Trial

The Prostate Cancer Prevention Trial (PCPT) is being conducted in the CCOP clinical trials network. The trial is an intergroup study involving over 225 community and university hospitals across the country. The study tests the ability of finasteride (Proscar), an inhibitor of androgen synthesis, to reduce the incidence of prostate cancer, the most common cancer in men. The PCPT will include approximately 18,000 men from across the United States. Participation is open to all men between ages 55 and 70. Black men and men with a family history of prostate cancer are being aggressively recruited because they may have the greatest risk of developing prostate cancer. The entire trial lasts 10 years and will include an evaluation of the benefit of annual prostate examinations and serial prostate-specific antigens (PSA) blood tests in detecting prostate cancers.

Screening for Prostate, Lung, Colorectal, and Ovarian Cancers (PLCO)

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) is a randomized, controlled clinical trial designed to determine whether particular screening modalities for prostate, lung, colorectum and ovary will reduce the number of deaths through early detection of these cancers. Over the next eight years this trial will randomize 148,000 participants with equal numbers of men and women ages 60-74 years. The risk of these cancers is high in this age group. The 37,000 men randomized to the intervention arm of the study will have a yearly digital rectal examination and a blood test for prostate-specific antigen (PSA) for prostate cancer, an annual chest x-ray for lung cancer, and a flexible sigmoidoscopy at the initial visit and another three years later for colorectal cancer. Equal numbers of women in the intervention group will receive an annual chest x-ray, and a sigmoidoscopy at the initial visit and another three years later, for lung and colorectal cancers respectively. For ovarian cancer screening, women will have an annual ovarian palpation, transvaginal ultrasound, and blood test for the tumor marker, CA-125. The pilot phase of the trial concluded in September of 1994 and a thorough evaluation of this phase will be completed in early 1995.

High and Low Risk Cervical Abnormalities

Over the past 40 years there has been a dramatic decrease in the incidence and mortality from cervical cancer in the U.S. This is due, in part, to early diagnosis and treatment of cervical cancer precursor lesions. However, the cost and morbidity associated with the detection and treatment of low-grade cervical lesions have escalated while the cancer prevention benefit remains unclear. In addition, there currently exists a lack of consensus in the medical community on the appropriate management of low-grade cervical cytologic abnormalities. Research is necessary to evaluate the proper management of these low-grade lesions and to develop new triage techniques for women with this diagnosis. An NCI-sponsored trial will test the hypothesis of whether HPV testing can be used to triage women with these low-grade lesions. The trial also includes a non-randomized evaluation of automated screening methods to improve the sensitivity of cervical cytology.

Behavioral and Psychosocial Research

As current health care practices emphasize disease prevention and early detection, many persons learn of their increased risk of cancer through general medical risk assessments, results of routine screening procedures or a diagnosis of cancer in a relative. Health care professionals are now recognizing the potential psychological impact and ethical implications of risk notification. NCI-sponsored research is evaluating specific counseling interventions to increase compliance with recommended therapy in newly-diagnosed cancer patients and increase adherence to early detection programs in persons notified of high risk of cancer. The initiative also focuses on improving quality of life in both of these groups.

NCI supports research for developing and testing techniques for measuring health-related quality of life in cancer patients from culturally diverse backgrounds. Instruments developed through this initiative will have immediate applications in cancer treatment. In addition, cancer clinical trials are adding quality-of-life endpoints to traditional outcome measures of tumor response, survival and toxicity. A research initiative directed at problems confronting young breast cancer patient is in progress as well.

Genetic studies of families with high incidence and prevalence of certain cancers has led to the identification of cancer-related genes. The acceptability of testing for heritable cancer risk and the psychosocial impact of risk notification are largely unexplored. To foster research in this area, the National Center for Human Genome Research, the National Cancer Institute, the National Institute of Mental Health, and the National Institute for Nursing Research will support studies of genetic testing and counseling for inheritable breast, ovarian and colon cancer risks.

SURVEILLANCE

NCI's Surveillance Program monitors the cancer burden on the U.S. population by measuring cancer incidence, mortality and survival and assessing individual, societal and health service factors that mediate these cancer measures. The ultimate purpose of cancer surveillance is to guide future programmatic and resource allocation decisions of the National Cancer Program.

A major component of the Program is the Surveillance, Epidemiology, and End Results (SEER) Program, which consists of 11 population-based cancer registries covering 14 percent of the nation's population. It is the largest single system for monitoring changes in cancer incidence, patient survival and mortality by geographic, demographic and social characteristics in the United States. Information on over 100,000 newly diagnosed cancer cases is reported each year through the SEER Program, along with follow-up status assessed annually for previously reported cases. Special short-term studies that draw on the SEER database as a resource for cancer control include among others: a study to investigate the effects of tamoxifen on subsequent risk of endometrial cancer in women for whom tamoxifen was used in the treatment of their breast cancer; and a study on prostate cancer and health-related quality of life following alternative treatments for clinically localized prostate cancer.

Studies linking SEER data with information from Medicare expenditure files provide vital information on cancer treatment patterns and the cost of cancer care by site and by stage. Economic studies on costs of cancer care play a significant role in cancer surveillance research. Several ongoing studies will provide a more complete assessment of the economic burden of cancer on the nation.

The U.S. breast cancer surveillance research database will complement efforts to establish an international database on breast cancer screening. Development of this database should provide an opportunity not only to assess effectiveness of screening programs but also to examine changes in health statistics on a national or regional level.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director.............	425	366	362
Division of Cancer Etiology.........	485	500	494
Division of Cancer Biology, Diagnosis, and Centers.............	497	493	487
Division of Cancer Treatment........	678	662	654
Division of Cancer Prevention and Control.......................	189	189	189
Division of Extramural Activities...	100	97	96
Frederick Cancer Research and Development Center............	8	8	8
Total, NCI	2,382	2,315	2,289

Average GS/GM Grade

1991...	10.3
1992...	10.3
1993...	10.3
1994...	10.7
1995...	10.6
1996...	10.6

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
ES-6			
ES-5	2	2	2
ES-4	13	8	8
ES-3	1	1	1
ES-2	3	3	3
ES-1	2	2	2
Subtotal	21	16	16
Total-ES Salary	$2,291,291	$1,801,609	$1,841,245
GS/GM-15	166	142	140
GS/GM-14	215	190	185
GS/GM-13	191	191	188
GS-12	239	242	237
GS-11	232	232	228
GS-10	3	3	3
GS-9	154	154	150
GS-8	78	78	77
GS-7	233	230	225
GS-6	103	103	100
GS-5	34	34	34
GS-4	14	14	13
GS-2	2	2	2
GS-1	1	1	1
Subtotal	1,665	1,616	1,583
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	2	2	2
Senior Grade	72	70	69
Full Grade	67	65	64
Senior Assistant Grade	62	60	59
Assistant Grade	29	28	28
Subtotal	233	226	223
Ungraded	112	104	103
Total permanent positions	1,798	1,736	1,702
Total positions, end of year	2,301	2,316	2,294
Total full-time equivalent (FTE) employment, end of year	2,382	2,315	2,289
Average ES level	3.2	3.2	3.2
Average ES salary	$109,109	$112,601	$115,078
Average GS/GM grade	10.7	10.6	10.6
Average GS/GM salary	$46,427	$49,366	$51,504

THURSDAY, MARCH 30, 1995.

NATIONAL CENTER FOR RESEARCH RESOURCES

WITNESSES

DR. JUDITH L. VAITUKAITIS, DIRECTOR
DR. LOUISE E. RAMM, DEPUTY DIRECTOR
RICHARD L. SHAFER, EXECUTIVE OFFICER
ANNE E. SUMMERS, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
WILLIAM BELDON, DIRECTOR, DIVISION OF PUBLIC HEALTH AND SOCIAL SERVICES BUDGET ANALYSIS, DHHS

Mr. PORTER. Our hearing now moves on to the National Center for Research Resources. The subcommittee is pleased to welcome Dr. Judith Vaitukaitis, Director.

Why don't you proceed in any way you choose, first introducing the people at the table with you.

INTRODUCTION OF WITNESSES

Dr. VAITUKAITIS. Thank you, Mr. Chairman.

I would like to introduce the person farthest to my left, Anne Summers, our Budget Officer; Richard Shafer, our Executive Officer; Dr. Louise Ramm, our Deputy; and of course you know Dr. Varmus, and Mr. Beldon was introduced earlier.

OPENING STATEMENT

Mr. Chairman and Members of the committee, it is a pleasure to tell you about the National Center for Research Resources' efforts to provide the tools and technologies that biomedical scientists need to make life-saving research advances. Most of NCRR's budget funds clinical, technological, and animal resource centers that serve as hubs for thousands of biomedical investigations each year. Those shared resource facilities serve more than 10,000 investigators.

Because most of these resources are shared, they leverage precious Federal research dollars, ultimately to improve the health of our Nation's citizens. NCRR shared resources promote collaborations across scientific disciplines and provide quick, flexible approaches to new and emerging research needs. Therefore, NCRR research-supported resources and activities collectively serve as a catalyst for discovery.

Today I will focus on how NCRR's resources and technologies are contributing to a series of scientific breakthroughs that have occurred with breathtaking speed. These discoveries transcend all areas of basic biology and clinical investigation and have given rise to novel clinical research tools to understand the molecular mechanisms of disease as well as to develop new therapeutic approaches, including gene therapy.

Much of the current clinical genetic and molecular biology research is taking place in a network of 75 General Clinical Research Centers. These GCRCs are playing a key role in gene therapy research and in a broad range of other approaches to treating and preventing disease. More than 7,000 investigators conduct nearly 5,000 clinical research projects annually. In the era of health care reform, the network of clinical research centers assumes an even more important role in assuring the translation of research advances to the patient.

Studies at GCRC sites not only define the underlying cause of disease, but also contribute significantly to the development of effective therapies for them. For example, investigators recently identified one candidate gene for familial breast cancer, BRCA–1, and narrowed the search for a second. In another study, researchers reported that, in addition to conventional genetic ties, the risk of Alzheimer's disease may also be linked to ethnic background.

In a different study, investigators at several GCRC sites contributed to a recently reported study that showed that giving the anti-AIDS drug zidovudine to pregnant women during the last two trimesters reduces HIV transmission to the newborn by two-thirds. And in late January NIH-supported scientists, many of whom carried out their studies at GCRCs, reported that hydroxyurea is an effective treatment for adults with sickle cell disease, an inherited blood disease that afflicts about 72,000 Americans, mostly African Americans.

High-quality and innovative biomedical research requires state-of-the-art instrumentation and technology. NCRR makes costly technologies available through its nationwide network of more than 60 biomedical research technology resource centers.

In this country, there has been a progressive increase in the use of synchrotron radiation facilities by biomedical investigators. Those facilities provide high-energy X-rays essential for determining the three-dimensional structure of proteins, nucleic acids, and viruses. These intense X-rays allow scientists to understand how damaged enzymes can cause uncontrolled cell growth and cancer. Seeing structures in such detail also facilitates design of new drugs to specifically intervene and control viral diseases like HIV and influenza, as well as other autoimmune diseases such as type-1 diabetes, multiple sclerosis, and rheumatoid arthritis.

Another way to share limited resources is to distribute them widely through "smart" network-connected technologies. For example, one can place a costly electron microscope in San Diego at the fingertips of investigators in Boston, Chicago, or Duluth—or any other sites on the Internet. The NCRR will extend its initial effort in this area to other computer-intensive technologies.

Instruments like mass spectrometers, image processors, protein/DNA sequencers, and cell sorters are crucial to research funded by NIH's categoric Institutes and Centers. One way to stretch the limited supply is for five to thirty scientists to share costly equipment through NCRR's shared instrumentation grant program. In fiscal year 1996, NCRR is requesting that the level of support for this program be increased to $18,800,000, an increase of $10,000,000, representing a commitment to this highly effective method of supporting sophisticated instrumentation for shared use.

Animal and other models are essential tools to define mechanisms of disease. NCRR supports a broad range of model systems. As science enters the 21st century, NCRR is developing new biotechnologies such as transgenic and knockout animals for species other than mice.

Legions of aquatic animals have been enlisted in the war against human disease. Studies of the abalone, a marine mollusc, have revealed that the death of unneeded cells is regulated by an orderly process called apoptosis or programmed cell death. Studies of abalone larvae may provide a useful new model for studies of development, aging, and diseases such as cancer, muscular dystrophy, and Alzheimer's. The NCRR will enhance its efforts in supporting marine technologies in fiscal year 1996 to take advantage of these less explored model systems that can help scientists better understand normal and disease-based processes which relate to human health.

Thus far, I have told you about shared clinical, technological, and animal resources needed to conduct biomedical research. But what about human resources? How can we ensure an adequate supply of well-trained investigators to learn and develop sophisticated molecular technologies so that approaches such as gene therapy can be brought more quickly to the bedside?

A recently published Institute of Medicine report, "Careers in Clinical Research: Obstacles and Opportunities," expresses concern about the numbers of physicians and dentists pursuing careers in patient-oriented research. In response, NCRR's GCRC program has expanded its successful Clinical Associate Physician programs to increase the pool of investigators who carry out NIH-supported patient-oriented research. NCRR will also initiate a Clinical Scholars Program designed to increase the supply of talented physicians to that pool. This program will serve as a bridge to junior career development and assure that these young investigators will be well versed in the basics of clinical research.

Finally, NCRR's new Clinical Research Infrastructure Initiative will provide clinical research training and junior career development for minority physicians and give them more opportunities to participate in clinical research, especially in studies of heart disease, diabetes, AIDS, and other major health problems facing minority populations.

To ensure that an adequate supply of investigators—especially minority scientists—enters the career pipeline, NCRR has since 1980 sponsored programs to attract high school students to careers in biomedical research and the health professions, giving thousands of students and their science teachers hands-on experience in biomedical research laboratories each summer. The programs also spur scientists to work with educators and other public sector organizations to improve student and public understanding of science and promote interest in science among students from kindergarten through high school.

Shared clinical, technological, animal, and human resources are the backbone of biomedical research infrastructure. If this infrastructure is not maintained, the enterprise it underpins—like a skyscraper without adequate steel beams—will weaken and eventually collapse. Ironically, we have entered a golden age of research that promises to revolutionize the way medicine is practiced. This opportunity may go unrealized if the resources scientists need to catalyze discovery are not available. NCRR's mission is to balance the equation by providing the tools investigators need to prevent, treat, and—as the molecular revolution promises—cure many common and rare diseases as well as to reduce health care costs in the future.

Mr. Chairman, the fiscal year 1996 budget request for the National Center for Research Resources is $316,544,000. I would be pleased to answer any questions you and your colleagues may have.

[The prepared statement and biography of Dr. Judith Vaitukaitis follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR RESEARCH RESOURCES
Statement of the Director

Mr. Chairman and Members of the Committee:

It is a pleasure to tell you about the National Center for Research Resources' efforts to provide the tools and technologies that biomedical scientists need to make life-saving research advances. Most of NCRR's budget funds clinical, technological, and animal resource centers that serve as hubs for thousands of biomedical investigations each year. Those shared resource facilities serve more than 10,000 investigators, supported by well over $1 billion of categorical institute funds. Because most of these resources are shared, they leverage precious Federal research dollars, ultimately to improve the health of our Nation's citizens. NCRR efforts also include development of specialized research models, "smart" network-connected technologies, computer-aided drug design, and bioengineering approaches to lower health care costs. Through enhanced training and career development for patient-oriented research, NCRR addresses the shortage of independent clinical investigators, including minorities. NCRR shared resources promote collaborations across scientific disciplines and provide quick, flexible approaches to new and emerging research needs in partnership with the other institutes and centers across the National Institutes of Health. Therefore, NCRR research-supported resources and activities collectively serve as a "catalyst for discovery."

Today I will focus on how NCRR's resources and technologies are contributing to a series of scientific breakthroughs in molecular biology and recombinant DNA technologies that have occurred with breathtaking speed. These discoveries transcend all areas of basic biology and clinical investigation and have given birth to novel clinical research tools to understand the molecular mechanisms of disease as well as to develop new therapeutic approaches, including gene therapy.

Much of the current clinical genetic and molecular biology research is taking place in a network of 75 General Clinical Research Centers that NCRR supports. These GCRCs are generally located in hospitals in academic medical centers across the U.S. GCRCs are playing a key role in gene therapy research and in a broad range of other approaches to treating and preventing disease. More than 7,000 investigators conduct nearly 5,000 clinical research projects annually. In the era of health care reform, the network of clinical research centers assumes an even more important role in assuring the translation of research advances to the patient.

Studies at GCRC sites not only define the underlying cause of acquired and inherited disease, but also contribute significantly to the development of effective therapies for them. For example, investigators recently identified one candidate gene for familial breast cancer, BRCA1, and narrowed the search for a second. In another study, researchers reported that, in addition to conventional genetic ties, the risk of Alzheimer's disease may also be linked to ethnic background. In a different study, investigators at several GCRC sites contributed to a recently reported study that showed that giving the anti-AIDS drug zidovudine to pregnant women during the last two trimesters reduces HIV transmission to the newborn by two-thirds. And, in late January, NIH-supported scientists, many of whom carried out their studies at GCRCs, reported that hydroxyurea is an effective treatment for adults with sickle cell disease, an inherited blood disease that afflicts about 72,000 Americans, mostly African-Americans.

Gene therapy, while still in its infancy, has the potential to correct an array of complex diseases and disorders that are either caused or affected by faulty genes. These include single-gene disorders such as cystic fibrosis, Gaucher disease, and the hemophilias. Multifactorial disorders such as melanoma and other cancers, hypertension, diabetes, heart and vascular diseases, pulmonary diseases, and AIDS are also thought to be amenable to gene therapy. Already, dozens of human gene therapy studies are under way to explore these possibilities. NCRR--in partnership with other NIH Institutes--has recently solicited applications for National Gene Vector Laboratories to ensure a safe and effective supply of vehicles--liposomes, modified viruses--to safely deliver genetic material into human somatic cells for the prevention, treatment and cure of a variety of diseases. This initiative will continue in FY 1996 and will also extend to studies in nonhuman primates. The full potential of gene therapy will not be realized for many years.

High-quality and innovative biomedical research requires state-of-the-art instrumentation and technologies. NCRR makes costly technologies available through its nationwide network of more than 60 biomedical research technology resource centers, including several which focus on major challenges within structural biology. For example, using high-performance computing as an enabling technology, several of those centers focus on understanding protein folding and the capacity to predict the tertiary structure--or three dimensional form--of a protein from its amino acid sequence. A new algorithm, which requires high performance computing, has been developed for that purpose.

In this country, there has been a progressive increase in the use of synchrotron radiation facilities by biomedical investigators. Those facilities provide high-energy x-rays essential for determining the three-dimensional structure of proteins, nucleic acids, and viruses. These intense x-rays allow scientists to understand how damaged enzymes can cause uncontrolled cell growth and cancer. Seeing structures in such detail also facilitates design of new drugs to specifically intervene and control viral diseases like HIV and influenza, and autoimmune diseases, such as type-I diabetes, multiple sclerosis, and rheumatoid arthritis. Improved x-ray sources, magnetic resonance imaging and spectroscopy, as well as mass spectrometers, combined with faster, more powerful computers, are allowing scientists to view biological systems--from molecules, subcellular organelles, and whole cells to organs--with greater sensitivity to better understand disease mechanisms.

Another way to share scarce resources is to distribute them widely through "smart" network-connected technologies. For example, one can place a costly electron microscope in San Diego at the fingertips of investigators in Boston, Chicago or Duluth--or any other sites on the Internet. The NCRR will extend its initial effort in this area to other computer-intensive imaging and microscopy technologies, virtual reality methods, and those biotechnology-related resources required for structure-based drug design.

Instruments like mass spectrometers, image processors, protein/DNA sequencers, and cell sorters are crucial to research funded by NIH's categoric institutes and centers. One way to stretch the limited supply is for 5 to 30 scientists to share costly equipment through NCRR's Shared Instrumentation Grant program. This year NCRR is requesting that the level of support for this program be increased to $18.8 million, an increase of $10 million, representing a commitment to this highly effective method of supporting sophisticated instrumentation for shared use.

NCRR has recently launched a new bioengineering initiative that is designed to stimulate research and development of novel, cost-effective microsensors, physiological monitoring systems, and "smart" drug delivery systems that could improve the quality and reduce the cost of health care, especially among the aged and disabled.

Animal and other models are essential tools to define mechanisms of disease and develop new preventive and therapeutic strategies. NCRR supports a broad range of model systems, including vertebrate, invertebrate, cellular, mathematical, computer, and physical models. As science enters the 21st century, NCRR is developing new biotechnologies such as transgenic and knockout animals for species other than mice. In FY 1993 NCRR funded the first National Resource for Transgenic Animals. This year, in response to the need of the scientific community, NCRR will expand its resources for transgenic and targeted mutant animals. With such precise models, it will be possible to study specific genes responsible for normal cell functions as well as for human diseases.

Legions of aquatic animals have also been enlisted in the war against human disease. Studies of the abalone, a marine mollusc, have revealed that the death of unneeded cells is regulated by an orderly process called apoptosis or programmed cell death. Studies of abalone larvae may provide a useful new model for studies of development, aging, and diseases such as cancer, muscular dystrophy, and Alzheimer's. The NCRR will expand its efforts in supporting marine technologies in FY 1996 to take advantage of these less explored model systems that can help scientists better understand normal and disease-based processes which relate to human health.

Thus far, I have told you about shared clinical, technological, and animal resources needed to conduct biomedical research. What about human resources? How can we insure an adequate supply of talented and well-trained investigators to learn sophisticated molecular technologies and develop new ones, so that approaches such as gene therapy can more quickly be brought to the bedside? A recently published Institute of Medicine Report--Careers in Clinical Research. Obstacles and Opportunities--expresses concern about the numbers of physicians and dentists pursuing careers in patient-oriented research. In response, NCRR's GCRC program has expanded its successful Clinical Associate Physician and Minority Clinical Associate Physician programs to increase the pool of investigators who carry out NIH-supported patient oriented research. NCRR will also initiate a Clinical Scholars Program, designed to increase the supply of talented physicians to that pool. The program will allow physicians or dentists completing postgraduate medical training to devote one year to intensive study of the basics of clinical research, bioethics, experimental study and clinical trials design, biostatistics, outcomes research, and other topics appropriate to future clinical research career goals. This program will serve as a bridge to junior career development and assure that these young investigators-to-be will be well versed in the basics of clinical research. In a separate effort GCRC sites will provide individuals in training and established clinical investigators with formalized courses in patient-oriented research and hands-on training in selected technologies for research for individuals in training as well as for established clinical investigators.

Finally, NCRR's new Clinical Research Infrastructure Initiative will provide clinical research training and junior career development for minority physicians and give them more opportunities to participate in clinical research, especially in studies of heart disease, diabetes, AIDS, and other major health problems facing minority populations.

To ensure that an adequate supply of investigators--especially minority scientists--enters the career pipeline, NCRR has since 1980 sponsored programs to attract high school students to careers in biomedical research and the health professions, giving thousands of students and their science teachers hands-on experience in biomedical research laboratories each summer. The programs also spur scientists to work with educators and other public sector organizations to improve student and public understanding of science and promote interest in science among students from kindergarten through high school.

Shared clinical, technological, animal and human resources are the backbone of biomedical research infrastructure. If this infrastructure is not maintained, the enterprise it underpins--like a skyscraper without adequate steel beams--will weaken and eventually collapse. Ironically we have entered a "Golden Age" of research that promises to revolutionize the way medicine is practiced. This opportunity may go unrealized if the resources scientists need to catalyze discovery are not available. NCRR's mission is to balance the equation by providing the tools investigators need to prevent, treat, and--as the molecular revolution promises--cure many common and rare diseases, and reduce health care costs in the future.

Mr. Chairman, the FY 1996 budget request for the National Center for Research Resources is $316,544,000. I would be pleased to answer any questions you may have.

CURRICULUM VITAE

Judith L. Vaitukaitis, M.D.
Director
National Center for Research Resources
National Institutes of Health

Birth place: Hartford, Connecticut

Education: B.S., Tufts University, 1962; M.D., Boston University School of Medicine, 1966; Internship and Residency, Second (Cornell) Medical Service, Bellevue Hospital, NY, NY, 1966-68; Medical Resident, University Hospital, Boston, MA, 1968-69; Academic Training Fellow, Boston University School of Medicine, 1968-71; Endocrine Section, National Cancer Institute, NIH, Bethesda, MD, 1970; Special PHS Postdoctoral Research Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971; Senior Staff Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971-73.

Professional History: March 1993 to present, Director, National Center for Research Resources (NCRR), NIH; 9/92 to 3/93, Acting Director, NCRR, NIH; 6/91 to 3/93, Deputy Director for Extramural Research Resources (ERR), NCRR, NIH; 2/15 to 6/3/90, Acting Deputy Director, ERR, NCRR; January 15 to February 15, 1990, Acting Deputy Director, Division of Research Resources; 6/91 to 11/92, Acting Director, General Clinical Research Centers (GCRC) Program, NCRR; 1986-1991, Associate Director for Clinical Research and Director, GCRC Program, NCRR; 1977-86, Professor of Medicine, Boston University School of Medicine (BUSM); 1980-86, Professor of Physiology, BUSM; 1974-86, Head, Section of Endocrinology and Metabolism, Boston City Hospital, Boston, MA.; 1975-86, Program Director, General Clinical Research Center, BUSM; 1977-80, Associate Professor of Obstetrics and Gynecology, BUSM; 1975-80, Associate Professor of Physiology, BUSM; 1974-77, Associate Professor of Medicine, BUSM; 1974-75, Guest Worker, Reproduction Research Branch (RRB), NICHD, NIH, Bethesda, MD; 1973-74, Senior Investigator, RRB, NICHD, NIH, Bethesda, MD.

Honors and Awards: 1987-1989, Associate Editor, Yearbook of Endocrinology; 1984-1986, Editorial Board, Endocrine Research; 1979-84, Editorial Board, Endocrine Research Communications; 1978-87, Editorial Board, Proceedings of the Society for Experimental Biology and Medicine; 1977-1985, Editorial Board, Archives of Andrology; 1973-1980, Editorial Board, Journal of Clinical Endocrinology and Metabolism; 1983, Distinguished Alumna Award, Boston University School of Medicine; 1980, Mallinckrodt Award for Investigative Research, Clinical Radioassay Society; 1983-86, General Clinical Research Centers Committee, Division of Research Resources; 1979-80, Population Research Committee Study Section, NICHD; 1977-80, Scientific Advisory Committee, Program for Applied Research on Fertility Regulation, Aid to International Development; 1975-78, Breast Cancer Task Force, Epidemiology Subcommittee, National Cancer Institute; Alpha Omega Alpha; Begg (honor) Society.

Publications: Author of over 160 scientific papers with four selected as Citation Classics; editor of one book.

EXTRAMURAL CONSTRUCTION

Mr. PORTER. Thank you, Dr. Vaitukaitis.

The fiscal year 1996 request includes $20 million for extramural facilities construction and renovation. As you know, the House has proposed to rescind this funding in fiscal year 1995 as one of NIH's contributions to deficit reduction. The committee was reluctant to reduce any fiscal year 1995 funding for NIH but felt that the extramural construction was a lesser priority than research grants. Part of our thinking was that the $20 million is not sufficient to make much of a dent in the infrastructure needs of universities.

What are the current estimates of need for research facility construction and renovation nationwide?

Dr. VAITUKAITIS. Based on a recently published NSF study on research facility needs for science and engineering, the estimates range as high as $10 billion. If one breaks it out, those needs that relate to biomedical research would be substantially less, something of the order of $2 billion to $4 billion probably. There are no good, accurate figures on this.

The greatest need probably relates to alterations and renovations of existing facilities that were built in the 1950s and early 1960s. In the construction program we have supported, which was initiated last year, most of the requests are for alterations and renovations to provide specialized facilities to handle dangerous viruses, or to modify laboratory animal facilities so that genetic manipulations of the animals could be carried out, or to address other special needs for facilities that are already in place rather than adding to existing facilities or expanding their capabilities.

Mr. PORTER. How much facility construction is supported through indirect cost reimbursement?

Dr. VAITUKAITIS. In the report from 1994 that has not yet been published by NIH, it is estimated that the alterations and renovations portion of indirect costs from fiscal years 1992 and 1993 is on the order of $657 million.

GENERAL CLINICAL RESEARCH CENTERS

Mr. PORTER. You support 76 General Clinical Research Centers and academic health centers across the country. As you observe the changes that they have made in their operations in response to tight budget constraints, do you think they have used any approaches that could be adopted by the NIH clinical center as it faces a downsizing environment?

Dr. VAITUKAITIS. The NIH clinical center has begun to adopt some of the approaches that the GCRCs were forced to initiate several years ago. They have consolidated research in-patient facilities for investigators across several different Institutes and Centers, which helps with reducing the staffing needs, a recurring cost which adds tremendously to operating any kind of clinical research facility.

In the extramural community, we have advantages they don't have in that we have direct access to patients. In the extramural community we have been allowed to markedly expand our outpatient-based research. In fact, for fiscal year 1993, for which we have our most recent data, there were over 220,000 outpatient research visits that were supported and about 120,000 inpatient research days. The NIH doesn't have that luxury. Referrals to the clinical center are from all over the country, but they have not been able to expand their outpatient-based research simply because of logistics, since their patients come from afar.

Research tools have changed markedly over the years. The average length of stay for a research patient on GCRCs is well below 3 inpatient days. The clinical center has also reduced its length of stay, but not quite as markedly, simply reflecting the fact that the mix of research at the clinical center is different from that across the GCRC network.

HIGH PERFORMANCE COMPUTING

Mr. PORTER. Your Center and the National Library of Medicine are the principal NIH participants in the high-performance computing initiative. One of the programs you are funding as part of the initiative is testbeds, which are supported at a cost of $1 million to $4 million each. Can you explain what these testbeds are and what applications they are experimenting with?

Dr. VAITUKAITIS. We are currently supporting no testbeds. We are planning to do that in the future. We have a testbed in planning, if you will, with the San Diego Computer Center and with the San Diego Microscopy Imaging Resource, which is tied to two different resources in Chicago and at another site.

The reason for developing this as a prototype is to make sure we get rid of all the bugs, if you will, so that an investigator in Chicago working at their computer work station can access the electron microscope in San Diego in real time and manipulate the microscope with his or her tools at the console in Chicago.

Mr. PORTER. That is what that is?

Dr. VAITUKAITIS. Yes. These would create virtual laboratories so that persons would not have to go physically to a site but could control things from their own institution with a cohort of sites carrying on complementary functions for a single research purpose.

Mr. PORTER. Are you excited about this technology?

Dr. VAITUKAITIS. Yes. This is going to revolutionize the way resource sharing can take place throughout the remainder of this decade and into the next.

SYNCHROTRON FACILITIES

Mr. PORTER. You mentioned in your testimony that you are supporting three synchrotron radiation facilities which provide high-energy X-rays to help researchers determine the three-dimensional structures of proteins and viruses. These facilities are very resource-intensive. Can you give us an idea of how much one of these facilities costs and the types of biomedical research for which they are important? Can you also tell us if the Department of Energy also contributes to the cost of the synchrotron facilities?

Dr. VAITUKAITIS. The Department of Energy contributes substantially to these facilities. In fact, we cannot afford to have these facilities ourselves. The cost of setting up one of these facilities in current dollars would be something of the order of about $100 million to $150 million. What we do in conjunction with the Department of Energy, and at one site with the National Science Foundation, is help build one or more beam lines at a facility. We currently have beam lines that are constructed and operational at Stanford, Cornell, and Brookhaven. We are in the process of building a new beam line at the Argonne advanced photon source.

These facilities are absolutely essential for understanding protein, viral, and nucleic acid structures. There has been a progressive use of these facilities by biomedical investigators. What generally happens is that physicists develop these technologies and then biophysicists and molecular biologists and biomedical investigators adapt those technologies to address key questions for biomedical research.

At the DOE facilities, one of the big problems has been a long waiting line for investigators to access these facilities. In fact, for every investigator accommodated, there are three that we cannot accommodate. Some of those investigators are accommodated by facilities in Europe and Japan, but those facilities are becoming more and more competitive and less accessible to our investigators.

In the fiscal year 1996 budget request for the Department of Energy, there is included a $100 million request for support of investigators to access synchrotrons on a more full-time basis. These facilities are supported for only about 6 months of the year in terms of the operational costs. The electric bill for these facilities is astronomic. For support of the electric bill alone at Stanford, for instance, it costs something on the order of $12 million to $14 million, let alone the staffing and other requirements.

Instead of building more facilities, it is wiser to extend the time of access for these facilities. In the DOE budget there is a provision to extend the amount of time during the year when these facilities operate, as well as increase the length of time these facilities run during the day. Instead of 8 hours, there will be two shifts in terms of DOE staffing.

The interface of DOE with other agencies is absolutely essential for us. We could not afford to even begin paying for this kind of facility ourselves.

Mr. PORTER. Thank you.

Mr. Bonilla?

Mr. BONILLA. Thank you, Mr. Chairman.

VIRTUAL REALITY

Doctor, I think the field you are working in is fascinating. I read about some of the advancements we are making with medical technology and the tools that doctors are using in this day and age.

In your budget justification, it states that national networks of resources would speed up the development of sophisticated instrumentation and biotechnologies—I am not sure if your agency is very involved in it—but enabling surgeons to hold single living cells. Also, this technology would have a tremendous impact in real-life circumstances in some cases where the environment is less than ideal, such as a battlefield or conducting open heart surgery.

I was looking at another item recently where they showed a doctor who was actually in one room manipulating these things almost like virtual reality and the probe that he is using in the next room is actually conducting the surgery.

Are you involved in some of that?

Dr. VAITUKAITIS. We are involved with that peripherally, using virtual reality for surgically related activities through our Small Business Innovative Research grants. We are also very heavily involved in using virtual reality for studying the way molecules interact and developing new drugs that interact with active sites and may make an enzyme more active or less active.

We are also using virtual reality to better understand the relationship between brain function and how we sense things and how we see things simultaneously. The technologies are here now so that we can integrate and synthesize many different sources of sensory input and understand that better. That kind of technology can result in better car design in terms of the ergonomics. It would also lead to better understanding of how to have patients undergo rehabilitation after central nervous system injury.

Mr. BONILLA. So that technology you just described on studying the brain—is that the same thing I see sometimes when thought processors are introduced to an individual and somehow they are read?

Dr. VAITUKAITIS. That would be part of the information. That technology, a result of magnetic resonance imaging, doesn't involve radioactive materials or contrast materials, but one can study selected parts of the brain. In fact, that technology has been modified with monitoring various metabolic end points to another form of magnetic resonance imaging, referred to as functional imaging, so that one can examine the different kinds of impacts of thought processes and visual contacts. All that integrates with the virtual reality system that I was describing a few minutes ago.

Mr. BONILLA. That's fascinating. I am surprised there hasn't been more reported on this.

Dr. VAITUKAITIS. It is relatively new.

Mr. BONILLA. You might see a documentary reflecting some of the great breakthroughs you all are working on.

Dr. VAITUKAITIS. Actually, the field that has contributed most to helping develop this whole area is Steven Spielberg's movies. They helped develop the technology itself. This has been picked up for biomedical research and has helped move that along tremendously.

Mr. BONILLA. Are you saying that Spielberg has contributed to this?

Dr. VAITUKAITIS. Yes, he has, ironically.

Mr. BONILLA. I have no further questions. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Bonilla.

Mr. Miller.

MINORITY PROGRAMS

Mr. MILLER. We've discussed this with Dr. Varmus before, but in your Center—concerning the role of minority programs and the money involved and all—I see that there is $22 million in your budget.

Describe the minority programs. Is this a set-aside? Is this competitive? How many institutions are available to go after this money?

Dr. VAITUKAITIS. All the money for our minority programs is competitive. The Research Centers at Minority Institutions is a program that was set up in 1985 to address the need for developing senior scientists who are minorities to address and help us interface with minority populations for clinical research. It is absolutely essential to bridge both clinical and basic research.

There are 19 RCMI institutions that are currently funded competitively. These are institutions that grant graduate degrees in medicine or in the biological life sciences. The institutions have to be at least 50 percent minority. We have RCMI institutions that are predominantly Hispanic. We have four in Puerto Rico as well as one at the University of Texas at San Antonio. Others serve mixtures of Hispanic and African American.

[CLERK'S NOTE.—Subsequent to the hearing, the location of the University of Texas RCMI program was corrected to El Paso.]

Mr. MILLER. There are 19 that are funded?

Dr. VAITUKAITIS. That's right.

Mr. MILLER. And they compete for that $22 million?

Dr. VAITUKAITIS. That is correct.

Mr. MILLER. Do they compete for the $108,000,000? Do they compete in the other areas, or do they just do their own?

Dr. VAITUKAITIS. The goal of the program is to help the investigators at those institutions become competitive for peer-reviewed funding from other components of the NIH. For instance, the currently funded 19 institutions, in 1984—the year before this program was started—collectively received $46 million in peer-reviewed support from NIH. In 1994, those same institutions have tripled the amount of funding they receive competitively from NIH.

Our goal is to bring them to a point where they become competitive and can work through other programs. The intent of the program is not to continuously support the same research. For instance, at Meharry Medical School, we support a neurosciences department. We supported them bringing on a lead scientist with junior faculty to develop a competitive grants program and help them develop a Ph.D. program for training minority scientists. In fact, they graduated two minority Ph.D.s a couple of years ago and they are the first two Ph.D.s in neurosciences to be graduated in this country.

In 1993, NSF published a study that examined the demographics of all doctoral graduates in the United States. Across the life sciences, there were 7,400 graduates. Of those, 2 percent were African American and 1 percent were Hispanic. But of those 2 percent, only 19 percent of that number were African Americans in the biological sciences. And of the 1 percent Hispanic, only 30 percent of them had earned Ph.D. degrees in biological sciences.

Minorities are marginally underrepresented in terms of the advanced degrees in this country for life sciences, particularly for biological sciences.

Mr. MILLER. But the program is mainly oriented toward institutions rather than individuals?

Dr. VAITUKAITIS. That is correct.

Mr. MILLER. An individual at the University of Florida would not be affected? They just affect a specific minority institution.

I see it has gone up over the years.

Dr. VAITUKAITIS. Yes. It has been relatively stable for the last couple of years. When it was started in 1985, there were about three or four institutions, and then a few more. Over the last few years, only one or two institutions have been added to the list.

As part of that program, there are three institutions that are funded to develop Ph.D. degree-granting programs in the biological sciences. The most recent one that was awarded was to the University of Texas at San Antonio.

[CLERK'S NOTE.—Subsequent to the hearing, the site of the most recently awarded science education RCMI grant was corrected to the University of Texas at El Paso.]

Mr. MILLER. What other minority programs are there besides that $22 million?

Dr. VAITUKAITIS. We have another program, the minority kindergarten to twelfth grade program, which was actually started, technically, in 1994. It is a changeover of our Minority High School Student Research Apprenticeship program which was begun in the early 1980s. In that program, the institutions eligible were based on how much NIH grant support they received from NIH. It was an administrative request for support.

We changed that program in 1994 to a competitive basis and phased in a new program, called the Minority K–12 Initiative. It will be fully phased in in fiscal year 1996. This program is for underrepresented minorities as well as their science teachers. It provides funding for up to 3 years on a competitive basis. It allows more flexibility to institutions to develop programs of their own. The previous program was only for summer research exposure. These other programs can be throughout the year. And, we have emphasized the inclusion of science teachers in this program because we believe we get a better leveraging effect from them.

Mr. MILLER. How much money is that program, for example?

Dr. VAITUKAITIS. That would be about $6 million. There is another $2 million for another science education program which is not directly minority-related, but includes a lot of minority teachers, called the Science Education Partnership Award program.

Mr. MILLER. So over 10 percent of your money is for set-asides for minorities?

Dr. VAITUKAITIS. It is 10 percent for minority-directed programs. We also have another program, the Minority Clinical Associate Physician program, which is competitive and which was begun in 1991. We anticipate supporting this year 15 clinical associate physicians who are designated as minorities by their institution. This is an effort to increase the number of minority physicians because we are having real problems recruiting underrepresented minorities into clinical trials and into other clinical research projects.

It is really important to have clinicians who are minorities and can relate to these individuals to bring them within the cohort. This is absolutely essential because, for instance, the underlying pathophysiology of hypertension in African Americans, is different from that of Caucasians. We can learn from both populations in terms of why those differences exist and how we can best treat them. This applies to many other diseases as well.

Mr. MILLER. The K–12 program—is it appropriate to be at NIH?

Dr. VAITUKAITIS. I believe it is. I believe it is important to have these youngsters understand science and what science is all about, not only to encourage some of them to become Ph.D.s or M.D.s but they may have to assume positions that are very technical with industry, and they have to have a strong science background. They have to understand about reasons why lifestyles need to be changed because they put them at risk.

This goes back to some of the conversation earlier this morning in terms of behavioral change. One has to inform youngsters about science and the risk factors for disease. If they learn that at a younger age, it is more likely that they will comply and alter their behaviors. A spinoff of this is also public science literacy so the public can make informed decisions about their lifestyles. In fact, some of our science education programs include youngsters along with their parents.

Dr. VARMUS. I would like to make one brief comment, Mr. Miller. Public education in the K–12 domain is not one of our primary missions, but we are concerned about recruiting a strong cadre of biomedical researchers in the future and about preparing the public for changes that are going to occur in health care and health prevention.

We are cognizant that our contribution in this area is relatively small. In fact, tomorrow our education office is hosting a meeting on the NIH campus of a number of people from other arenas who are contributing to changes in science education in the K–12 arena. We are looking to those folks for suggestions on how we can best use the relatively small amount of money NIH spends in this area so that we make good use of health as a vehicle for drawing students into scientific careers.

Mr. MILLER. The day we were at NIH, because of a budget meeting I missed the presentation on the minority program. Overall, how much is set-aside? Do you know?

Dr. VARMUS. I am not sure I would like to use the term "set-aside".

Mr. MILLER. Isn't that what it is?

Dr. VARMUS. Not entirely because in many cases we are talking about expenditures for what we call initiatives to study certain diseases that happen to afflict minority populations in particular, for example, sickle cell disease or certain components of renal disease, hypertension. If we look at our total expenditures for minority health overall at NIH, it is $1.2 billion. But as was mentioned, these are competitive programs. They address what we see as health needs because of the special illnesses that affect a minority population or because of discordances between the progress that has been made on certain diseases and different populations.

So we consider these to be competitive programs that happen to address concerns that affect a very large proportion of our population.

Mr. MILLER. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Miller.

Dr. Vaitukaitis, we have a number of additional questions we are going to put in the record.

You may believe that since we spent less real time with you than we did with the National Cancer Institute that we didn't cover as much ground, but your answers were so quick and so efficient that we actually covered equally as much ground. [Laughter.]

We very much appreciate your very candid, direct, and detailed responses and the fine work that you do there at the Center and for our country. Thank you for coming to testify.

Dr. VAITUKAITIS. Thank you.

Mr. PORTER. We will stand in recess until 2:00 p.m. this afternoon.

[The following questions were submitted to be answered for the record:]

BIOMEDICAL RESEARCH SUPPORT

Mr. Porter: Does the 1996 request include any funding for biomedical research support grants? Provide a breakout of the components of the request for "biomedical research support."

Dr. Vaitukaitis: The Biomedical Research Support Grant component of the National Center for Research Resources' Biomedical Research Support Program was discontinued in Fiscal Year 1992.

The components of the Fiscal Year 1996 Biomedical Research Support Program (including AIDS) are as follows (dollars in thousands):

ACTIVITY	# AWARDS	AMOUNT
Shared Instrumentation Grants	98	$20,500
K-12 Program		6,414
SEPA	20	2,000
IDeA	13	1,100
TOTAL	131	$28,355

Shared Instrumentation Grants and the K-12 Program comprise the biomedical research support mechanism.

FUNDING FOR SPECIFIC PROGRAMS

Mr. Porter: Identify 1994-1996 funding for the following: IDeA, Minority High School Student Research Apprentice Program, shared instrumentation grants, primate centers, and extramural animal facility renovation.

Dr. Vaitukaitis: The 1994-1996 funding (including AIDS) for IDeA, Minority High School Student Research Apprentice Program (MHSSRAP), shared instrumentation grants, primate centers, and extramural animal facility renovation is as follows (dollars in thousands):

ACTIVITY	1994	1995	1996
IDeA	$ 785	$ 1,100	$ 1,100
MHSSRAP/K-12 Program*	8,818	7,253	6,414
Shared Instrumentation Grants	9,001	9,500	20,500
Primate Centers	42,581	43,724	44,474
Animal Facilities Improvements	3,813	3,817	3,817

*The Minority High School Student Research Apprentice Program will be phased out after Fiscal Year 1995 and replaced with a competitive program for K through 12 teachers and high school students.

BIOMEDICAL RESEARCH TECHNOLOGY CENTERS

Mr. Porter: Identify the biomedical research technology centers funded in 1995 by type of center.

Dr. Vaitukaitis: Following is a list of biomedical research technology centers supported in 1995:

ADVANCED COMPUTATION - HIGH PERFORMANCE COMPUTING

General Atomics
University of California, San Diego
San Diego, CA
Biomedical Computation Resource

MPC Corporation
Pittsburgh, PA.
Supercomputing for Biomedical Research

University of Illinois Urbana-Champaign
Urbana, IL.
Resource for Concurrent Biological Computing

Washington University
St.Louis, MO.
Resource for Biomedical Computing

University of Minnesota Twin Cities
Minneapolis, MN.
Simulation Resource for Stochastic Population Models

University of Rochester
Rochester, N.Y.
Resource for the Study of Neural Models of Behavior

University of North Carolina Chapel Hill
Chapel Hill, N.C.
Interactive Graphics for Molecular Studies

University of California San Francisco
San Francisco, CA.
Research Resource in Biomolecular Graphics

University of Washington
Seattle, WA.
Resource Facility for Kinetic Analysis

Columbia University
New York, N.Y.
Theoretical Simulation of Biological Systems

1990

Cornell University
Ithaca, N.Y.
Parallel Processing Resource for Biomedical Scientists

MCNC
Research Triangle Park, N.C.
Parallel Computing Resource for Structural Biology

BIOENGINEERING

University of Washington
Seattle, WA.
Simulation Resource in Mass Transport and Exchange

University of Southern California
Los Angeles, CA.
Biomedical Simulations Resource

Drexel University
Philadelphia, PA.
Computer Vision Center for Vertebrate Brain Mapping

Cornell University
Ithaca, N.Y.
Biotechnology Resource Digital Electro-Optical Imaging

John Hopkins University
Baltimore, MD.
Biocalorimetry Center

University of Washington
Seattle, WA.
Surface Analysis Facility for Biomedical Problems

University of Michigan at Ann Arbor
Ann Arbor, MI.
Center for Neural Communication Technology

University of California Irvine
Irvine, CA.
Laser Microbeam Biotechnology Resource

Massachusetts Institute of Technology
Boston, MA.
Laser Biomedical Research Center

MOLECULAR TECHNOLOGIES

MASS Spectrometry

Massachusetts Institute of Technology
Boston, MA.
Mass Spectrometry Facility for Biomedical Research

1991

University of California San Francisco
San Francisco, CA.
Bio-Organic Biomedical Mass Spectrometry Resource

Rockefeller University
New York, N.Y.
Mass Spectrometry of Biological Macromolecules

Washington University
St. Louis, MO.
Biomedical Mass Spectrometry

Michigan State University
East Lansing, MI.
Mass Spectrometry

University of Georgia
Athens, Georgia
Resource Center for Biomedical Complex Carbohydrates

Magnetic Resonance -- In Vivo

Carnegie-Mellon University
Pittsburgh, PA.
Multidisciplinary NMR Center for Biomedical Research

Duke University
Durham, N.C.
Integrated Center for in vivo NMR Microscopy

University of Illinois Urbana-Champaign
Urbana, IL.
Biomedical Magnetic Resonance Research and Technology

University of Pennsylvania
Philadelphia, PA.
Resource for Magnetic Resonance and Optical Research

University of Texas SW MED CTR/Dallas
Dallas, TX.
Southwestern Biomedical Magnetic Resonance Facility

University of Florida
Gainsville, FL.
NMR Imaging and Spectroscopy in vivo Resource

University of Alabama at Birmingham
Birmingham, AL.
Clinical NMR Studies at 41T

University of Minnesota Twin Cities
Minneapolis, MN.
NMR Imaging and Localized Spectroscopy

1992

Stanford University Medical Center
Stanford, CA.
Lucas Center for Magnetic Resonance

MOLECULAR TECHNOLOGIES

Magnetic Resonance - Other Molecular Spectroscopies

University of Wisconsin Madison
Madison, WI.
National Biomedical NMR Resource

Massachusetts Institute of Technology
Boston, MA.
Center for Magnetic Resonance

University of Pennsylvania
Philadelphia, PA.
Resource for Solid-State NMR of Proteins

Yeshiva University
New York, N.Y.
Biotechnology Resource in Pulsed EPR Spectroscopy

Oklahoma Medical Research Foundation
Oklahoma City, OK.
Spin Trapping Free Radical in Biology and Medicine

University of Illinois Urbana-Champaign
Urbana, IL.
Electron Spin Resonance Center

Medical College of Wisconsin
Milwaukee, WI.
National Biomedical ESR Center

University of Maryland at Baltimore
Baltimore, MD.
Center for Fluorescence Spectroscopy

University of Illinois Urbana-Champaign
Urbana, IL.
Laboratory for Fluorescence Dynamics

University of Pennsylvania
Philadelphia, PA.
Ultrafast Optical Processes Laboratory

X-RAY TECHNOLOGIES

Cornell University Ithaca
Ithaca, N.Y.
Macromolecular Diffraction Resource--Macchess

Stanford University
Stanford, CA.
Synchrotron Radiation Biotechnology

University of California San Diego
San Diego, CA.
Resources for Protein Crystallography

University of Chicago
Chicago, IL.
BIOCARS--A Synchrotron Structural Biology Resource

ADVANCED MATERIALS

University of Calif-Los Alamos Nat. Lab.
Los Alamos, NM.
Stable Isotope Resource at Los Alamos

University of California, Berkeley
Berkeley, CA
National Tritium Labelling Facility

CELLULAR TECHNOLOGIES

University of Calif-Los Alamos Nat Lab
Los Alamos, NM.
National Flow Cytometry and Sorting Research Resource

Marine Biological Laboratory
Woods Hole, MA.
National Vibrating Probe Facility

Baylor College of Medicine
Houston, TX.
3-D Electron Microscopy of Macromolecules

University of California San Diego
San Diego, CA.
Southwestern Regional IVEM and Image Analysis Resource

University of Colorado at Boulder
Boulder, CO.
3 Dimensional Fine Structure of Cells and Tissues

University of Pennsylvania
Philadelphia, PA.
Regional IVEM and Image Analysis Resource

Wadsworth Center for Laboratories and Research
Albany, N.Y.
Biological Microscopy and Image Reconstruction Resource

Associated Univ-Brookhaven Natl Lab
Brookhaven, N.Y.
STEM Mass Mapping & Heavy Atom Labeling of Biomolecules

University of Wisconsin Madison
Madison, WI.
Integrated Microscopy Resource for Biomedical Research

Louisiana State Univ. Med. Ctr. New Orleans
New Orleans, LA.
Human Genetic Analysis Resource

Cold Spring Harbor Laboratory
Cold Spring Harbor, N.Y.
Resource for Construction of 2D Gel Protein Databases

SHARED RESOURCES

Mr. Porter: Dr. Vaitukaitis, you indicate in your statement that the shared resources supported by your Center serve more than 10,000 researchers. It may be an impossible question to answer, but have you ever tried to calculate the additional cost to NIH if each of these researchers sought funding for the shared resources independently?

Dr. Vaitukaitis: I can provide estimates for cost savings for selected activities. For example, in FY 1994, NCRR made 45 shared instrument grant awards, totalling $9.0 million, with an average award of $200,000; each award was to support an average of 14.3 scientists. Therefore, if one were to provide each of those investigators that same scientific equipment, the total cost would have been $ 128.7 million for that fiscal year. The total savings would be about $120 million. Even if the equipment were purchased for only four investigators, the savings would have been about $21 million.

The network of 75 General Clinical Research Centers supported about 7,000 investigators in FY 1994 at a cost of $136.6 million. Conservatively, the GCRCs save one-third to one-half of the patient-research based costs for clinical research at those facilities. In addition to cost leveraging, the paramedical personnel -- research nurses, core laboratory technicians -- facilitate research for both the research participants and investigators; the cost savings for that aspect of GCRCs are immeasurable.

Considerable cost savings accrue across our Biotechnology Resource Centers as well. Several of those centers would never exist for a single or even a dozen scientists - for example, the synchrotron resources for high energy X-ray exploration of protein, viral or DNA structure. Some types of these centers would cost three hundred percent more if they were not shared among a number of investigators. Overall, we estimate that the biotechnology resource centers save NIH over $3 billion by providing shared rather than individual facilities. In addition, the expertise provided to aid researchers in the use of the technologies is invaluable.

Another example of cost saving resources is the National Cell Culture Center. This organization provides large-scale cell culture and monoclonal antibodies to researchers. The monoclonal antibodies wouldcost about 42 times as much if they had to be purchased from commercial vendors. If researchers had to set up their own culture laboratories to produce large-scale cell cultures, it would cost even more.

SHARED INSTRUMENTATION

Mr. Porter: Your budget reflects as one of its priorities increased funding for the shared instrumentation program. Instrumentation has also been mentioned as a concern by some of the outside groups, such as the medical schools. Can you tell us why instrumentation is identified by the research community as a high priority need, compared to other areas you support?

Dr. Vaitukaitis: Sophisticated instrumentation is a prerequisite for cutting-edge research. In order to keep the U.S. biomedical research enterprise competitive in the global research arena it is imperative that our investigators have the very best instrumentation available to them. Unfortunately, due to severe budget constraints, the availability of such equipment has been drastically reduced.

In FY 1992, the funds for the SIG program were cut from $32.5 million to $8.75 million which resulted in a proportional reduction in the number of awards from 160 per year to 40. With the current constraints on the NIH budget, the level has remained at $8 million for the last 3 years. The consequence is that NIH investigators are having to do research with aging instruments and a pent-up need exists for an array of new modern instruments to help them maintain quality research projects. The NCRR is requesting an additional $10 million to help address this need.

Mr. Porter: What is the average cost of the equipment supported by the shared instrumentation program? Could such costs be reimbursed under regular research grant applications?

Dr. Vaitukaitis: The average cost of shared instrumentation grants is $200,000. This compares to an NIH-wide average cost of a research project grant award of about $261,000 estimated for FY 1996.

Today's health-related research requires access to modern state-of-the-art equipment. The funds provided in this program range from $100,000 to $400,000 per grant. The cost of the advanced instrumentation and the fact that it must be regularly updated or replaced make it much too costly to be justified through the regular research grant mechanism.

CLINICAL RESEARCH

Mr. Porter: We have been told that extramural clinical research is under threat because of its cost in an era when managed care makes absorbing the uncompensated costs of clinical research more difficult. Do these same pressures affect your general clinical research centers?

Dr. Vaitukaitis: Yes, these same pressures affect our General Clinical Research Centers (GCRCs). Most of the GCRCs are located at academic medical centers. Because managed care often focuses on cost containment, it is less expensive to send patients to primary care physicians at local community hospitals rather than to specialists at academic medical centers. Managed Care Organizations frequently arereluctant to have their patients in clinical research, let alone pay for established medical care costs. This is having a negative impact on clinical research.

Mr. Porter: One of the ideas suggested at the NIH Director's Advisory Council meeting in December was the use of your clinical research centers as "nodes" for telemedicine links to the NIH Clinical Center, so that initial patient evaluations could be conducted long-distance. Is this concept being pursued? Are your clinical research centers among the leaders in the use of telemedicine?

Dr. Vaitukaitis: Yes, the concept of GCRCs as "nodes" for telemedicine links to the NIH Clinical Center is under consideration, so that initial patient evaluations could be conducted "long-distance." Under this concept, prospective patients for a study at the NIH Clinical Center could first be evaluated at a local GCRC to see if their medical condition really qualified them to participate in that study, sparing them an initial "work-up" trip to Bethesda. Many multi-center trials are being conducted at a number of GCRCs, and data is transmitted from one GCRC to another, making the GCRCs among the leaders in the use of telemedicine.

GENE VECTOR LABORATORIES

Mr. Porter: You have begun a gene vector lab initiative in cooperation with several NIH institutes. Why are gene vectors most productively studied on a multi-institute basis? Is it complexity, cost, or other factors?

Dr. Vaitukaitis: The Request for Applications for the National Gene Vectors Laboratories is a cooperative venture of NCRR, NCI, NHLBI and NIDDK. These four organizations have agreed to share the costs because of the great promise of gene therapy for treatment of diseases of interest to these organizations. It is cost effective for these NIH components to share the costs of common facilities, rather than each independently funding such a venture. This approach will provide standardized reagents for use in multi-center trials. Diseases thought to be amenable to gene therapy include, but are not limited to, single gene disorders such as cystic fibrosis, Gaucher disease, adenosine deaminase deficiency, immune deficiencies, hemoglobinopathies, hemophilias, hypertension, diabetes, heart disease, and pulmonary diseases. In addition, diseases such as acquired immunodeficiency syndrome (AIDS) and malignancies require suitable vector development, production, and distribution to enhance research leading to effective treatment. Gene therapy for such diseases requires the development of suitable vectors to transfer new genetic material to target cells. Somatic cells such as lung, muscle, liver, neuronal, and bone marrow stem cells, as well as tumor cells, are important targets for gene therapy. An array of viral vectors are under investigation for use in such treatments.

Mr. Porter: In earlier NIH testimony, we have heard the issue of vectors described as one of the principal challenges to effective gene therapy. Is the science of vectors currently at a fairly elementary level?

Dr. Vaitukaitis: Yes, one might say that the science of vectors is currently at a fairly elementary level. But rapid strides are being made. We expect that in the near future, improved vectors will be even safer and more efficient at delivering genetic material into human cells, furthering the ability to more safely and effectively carry out gene therapy for both single- and multiple-gene disorders.

ANIMAL FACILITY IMPROVEMENT

Mr. Porter: You have financed animal facility renovations for some time, in part in response to more rigorous government standards for animal care. Do you feel we have reached an appropriate balance between humane treatment of research animals and the cost of compliance, or should this be an area of attention as deregulatory efforts continue?

Dr. Vaitukaitis: The NCRR has administered a competitive grant program for some time to upgrade animal facilities and develop centralized programs of animal care. This support has assisted institutions in their efforts to comply with the Animal Welfare Act and other policies related to the care and use of laboratory animals. The need for improvement and modernization of research animal facilities extends well beyond the needs that can be addressed through the 10 to 15 awards per year that this program currently provides. We do not anticipate any reductions in Federal regulations related to the health, humane care and overall welfare of laboratory animals, and view the continuation of a matching grant facilities program as an important priority.

A national survey of animal facilities at approximately 1,000 institutions is currently being done. This survey will provide important information regarding the status of current animal care and housing across the nation, and also address future needs and estimated costs. The survey is to be completed in about a year.

BIOENGINEERING INITIATIVE

Mr. Porter: Can you explain for us your new bioengineering initiative and how it may contribute to reduced health care costs?

Dr. Vaitukaitis: NCRR has launched a new effort to stimulate research and development of novel, cost-effective bioengineering approaches to the prevention, treatment or rehabilitation of disease or disabling conditions. Initial investments are in three areas: micro-sensors, physiological monitoring and drug delivery systems. Emphasis is on innovation, sound scientific engineering and medical rationale and must be assessed to generate reductions in health care costs. We will provide $1 million from the NCRR and $1 million will be used from the Whitaker Foundation to support approximately 8 of these applications this fiscal year.

The potential benefit of this research will lead to both improved health and reduction in health care costs, especially among the aged and the disabled.

NCRR REORGANIZATION

Mr. Porter: Can you describe the major reorganization of your Center that is underway? Was the need to reduce staffing the primary motivation for the reorganization?

Dr. Vaitukaitis: The NCRR is in the process of realigning its extramural programs to provide greater efficiency and better interactions among related activities. When accomplished, we will have reduced from seven programs to four. Although the need to reduce staffing was a consideration in the reorganization, that need was not the primary driving force behind the change.

SHARED EQUIPMENT

Mr. Porter: Can you clarify for us the difference between the type and cost of shared equipment available through your biotechnology centers versus the shared instrumentation grant program?

Dr. Vaitukaitis: Typical regional or national Biomedical Technology Centers are designed to support the development of new, emerging technologies and instrumentation which can expand or extend the current capabilities of commercially available instruments. The staff at these facilities identify new advanced technologies and adapt or modify them for biomedical research needs, thus expanding the technological boundaries of existing instruments and opening up new areas in biomedical research.

With time, many of the experimental instruments become commercially available, user-friendly and less costly and become routine instruments for biomedical research. The Shared Instrumentation Grant (SIG) Program acts as a technology transfer vector by directly providing institutions with a broad cross-section of basic and clinical NIH-funded investigators. This new sophisticated instrumentation which has new heights of sensitivity, flexibility and computational power provides NIH grantees with unparalleled opportunities to resolve fundamental problems on the cause and cure of human disease.

For example, a 600 MHz Nuclear Magnetic Resonance (NMR) spectrometer, considered a prototypical instrument first developed at a Biomedical Technology Resource Center at Carnegie Mellon University a few years ago, is now commercially available to biochemistry laboratories and is being provided to groups of NIH investigators through the SIG program. The Biomedical Technology Centers now provide for the new state-of-the-art instrument for NMR spectroscopy at 750 MHz. Most of the instruments provided by the SIG Program are in the $100,000 to $400,00 cost range (DNA sequencers, cell sorters, confocal microscopes, etc.) but some, such as Mass Spectrometers and NMRs, exceed the $400,000 limit. For the Biotechnology Resource Centers some of the instrumentation, for example synchrotrons or some high performance computers, are one-of-a-kind or rare devices whose price tags are in the many millions of dollars.

INSTITUTIONS INFRASTRUCTURE

Mr. Stokes: Extensive concern continues regarding the need to strengthen clinical research infrastructure at minority institutions. In response to congressional concern, I understand that plans are underway to address this concern through a collaborative effort between the Research Centers in Minority Institutions (RCMI) and the General Clinical Research Centers (GCRC) Programs. To what extent does the Center have plans and initiatives underway to address this ongoing problem?

Dr. Vaitukaitis: The GCRC and RCMI Programs of NCRR have been involved in a collaborative planning process to establish an enhanced clinical research capability at RCMI grantee institutions involving minority medical schools. The concept builds on the recognized success of the RCMI Program in enhancing biomedical research capacity and competitiveness in the basic sciences. The long range goal is to increase the number of minority physician clinical investigators and increase the number of minorities participating in clinical research projects, especially for those diseases that disproportionately impact minorities. Five of the eight medical schools participating in the RCMI program have submitted applications for this clinical research infrastructure initiative and are currently under review. NCRR expects to issue three or four awards for up to five years. Collaboration between these institutions and GCRC grantees is being encouraged.

Mr. Stokes: Initiated in 1985, the RCMI Program has proved to be a successful Program. Are there plans to evaluate this program in order to monitor its success or the need to change its focus?

Dr. Vaitukaitis: We believe that this is a most appropriate time to evaluate the RCMI Program, since many of the grantee institutions have now participated in this program for nine or ten years. The first phase of an evaluation process will begin soon. The evaluation will be structured to address major program accomplishments and to identify areas where improvements or changes may further facilitate the achievement of RCMI program goals.

INDIRECT COST

Mr. Stokes: As you know there has been tremendous concern with regard to escalating indirect cost at research institutions. What is the proportion of indirect to direct cost of research grants? What portion of the indirect cost amount is used by institutions to strengthen their infrastructure? What might the strengthening of infrastructure include?

Dr Vaitukaitis: For FY 1996, we estimate that indirect costs will represent approximately 30.9 percent of NIH's total award dollars. Although indirect costs are being described in terms of facilities costs and administrative costs, facilities costs, which include depreciation and use allowances, interest on debt associated with certain buildings, equipment and capital improvements, operations and maintenance expenses and library expenses, do not fund new construction and renovation. A portion of facilities costs are paid to reimburse the recipient organization for expenses already incurred for facility costs. These costs are paid as a depreciation or use allowance based on standard accounting practices for the use of the physical plant and equipment that is devoted to the conduct of research.

However, OMB Circular A-21 does require that institutions' payment for depreciation or use allowance made under sponsored research agreements be expanded to acquire or improve research facilities within five years. The weighted average for depreciation and use allowance is approximately 8 percentage points of the overall weighted average rate of approximately 51 percentage points. The amount of indirect costs paid as depreciation and use allowance for both space and equipment in FY 1994 was approximately $186 million.

Mr. Stokes: What is the average rate of indirect cost on research grants funded at Historically Black Colleges and Universities?

Dr. Vaitukaitis: The average rate of indirect cost across the NIH for FY 1994 is 26.3 percent of the total cost for awards to historically black colleges and universities.

PIPELINE

Mr. Stokes: I understand that the Center supports a minority high school program that has now evolved into a kindergarten through grade twelve initiative. How did this program evolve? Also, how is the Center addressing the need to develop more minority clinical investigators?

Dr. Vaitukaitis: The Minority High School Student Research Apprentice Program (MHSSRAP) has been supported by NCRR since 1980 and continues as NIH's flagship program for attracting high school students to careers in biomedical research and the health professions, providing six to eight week summer hands-on research experiences in active biomedical laboratories for high school students. The activity has grown from approximately 1,000 students per year for the first 10 years to between 2,000 to 3,000 students per year since 1990. For the past three years, the program has progressively expanded to include summer training experiences for K-12 teachers. In FY 1992 and 1993, 1,071 elementary, middle and senior high school teachers had the opportunity to update their skills in modern research tools and techniques. In FY 1993, the program was further expanded to include potential K-12 teachers in pre-service education programs. Given its important goal of increasing the pool of minority youth interested in careers in the health professions and the expansion in program activities over the years, the MHSSRAP has been converted into a new competitively peer-reviewed program, the "NCRR Minority Initiative: K-12 Teachers and High School Students," which better describes its current mission and assures support for the highest priority proposals.

The GCRC Program, NCRR has always encouraged increased participation of minority clinicians in medical research. For over a decade, these efforts have been augmented by collaborative arrangements between GCRCs and minority medical schools (Meharry/Vanderbilt and UCLA-Harbor/Drew are but two examples) and by the participation of clinicians from both minority and majority institutions in individual research protocols. In addition, the Minority Clinical Associate Physician (MCAP) Program of the GCRC Program, which is specifically designed to enable minority physicians to become independent clinical investigators, has expanded significantly in recent years.

Finally, the NCRR is implementing a new clinical research infrastructure initiative for RCMI-eligible institutions with medical school components which will provide opportunities for clinical investigations by physicians in these minority communities. The resources made available through this initiative are expected to be a significant factor in substantially increasing the numbers of minority clinical investigators.

COST BENEFIT

Mr. Stokes: According to your opening statement, the Center's efforts include development of specialized research models, "smart" network-connected technologies, computer-aided drug design, and bioengineering approaches to lower health care costs. With respect to the bioengineering approaches that have contributed to lowering health care costs, how extensive is the initiative? What have been the most significant medical technology spin-offs and payoffs from the Nation's investment in the Center's bioengineering activities?

Dr. Vaitukaitis: NCRR has launched a new effort to stimulate research and development of novel, cost effective bioengineering approaches to the prevention, treatment or rehabilitation of disease or disabling conditions. Initial investments are in three areas: microsensors, physiological monitoring and drug delivery systems. Emphasis is on innovation, sound scientific engineering and medical rationale, and must be assessed to generate reductions in health care costs. NCRR and the Whitaker Foundation will each provide $1 million to support approximately 8 of these applications in fiscal year 1995. The potential benefit of this research will lead to both improved health and reduction in health care costs, especially among the aged and the disabled.

Examples of other medical technology spin-offs and payoffs from NCRR's bioengineering activities include basic research and development in the following areas: magnetic resonance imaging (MRI); therapeutic and surgical application of lasers; development of new classes of sensors used to monitor patient oxygen levels and level of acidity in a non-invasive manner; and greater knowledge about the interface between biomaterials and tissues (for example, assessing the best materials for use in contact lenses and ocular implants). For MRI, developments in fast imaging will provide for shorter imaging times for the patients and greater through-put to very expensive machines. Functional imaging will allow monitoring of such functions as rates of blood flow thru tissues or metabolic state of tissues to determine specific areas of brain damage or the extent of brain tumor formation or epilepsy. These procedures can be performed without addition of contrast agents to the patient and without exposure to x-ray radiation.

AIDS AND BREAST CANCER

Mr. Stokes: What is the Center's role in the NIH's AIDS and breast cancer research initiatives?

Dr. Vaitukaitis: Through the provision of a comprehensive range of human, animal, technological, and other resources, the National Center for Research Resources (NCRR) promotes collaborations within and across scientific disciplines and NIH institutes. NCRR resources provide quick, flexible approaches to new and emerging research needs, such as AIDS and breast cancer research.

In cooperation with the AIDS Clinical Trials Group (ACTG), investigators at NCRR-supported resources continue to devote major efforts and resources to test drugs that may be effective against HIV or complications of AIDS.

Significant discoveries occurred in two major multicenter ACTG studies, partially conducted at NCRR supported resources. The first study found that in pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during pregnancy, a regimen consisting of zidovudine given ante partum and intra partum to the mother and to the newborn for six weeks reduced the risk of maternal-infant HIV transmission by approximately two thirds. The second study found that intravenous immune globulin decreases the risk of serious bacterial infections in children with advanced HIV disease who are receiving zidovudine. However, this benefit is apparent only in children who are not receiving trimethoprim-sulfamethoxazole as prophylaxis.

An animal model system provides a better understanding of maternal-fetal transmission of simian immunodeficiency virus and permits the evaluation of potential therapeutic agents to control HIV infection.

The NCRR General Clinical Research Centers (GCRC), frequently located in urban areas of intense research activity, are uniquely positioned to collaborate and contribute to the diffusion of AIDS clinical trial research. Forty-seven of the 74 GCRCs are involved in AIDS clinical trial research. A major National Eye Institute clinical trial of treatment of cytomegalovirus (CMV) retinitis was conducted at eleven GCRCs across the country which compared the two drugs ganciclovir, which was considered the primary drug for CMV retinitis, and foscarnet. Results suggest that for patients with AIDS and CMV retinitis, treatment with foscarnet provides a survival advantage over treatment with ganciclovir.

The NCRR resource funding for a Puerto Rico HIV/AIDS research program has made significant impacts on the improvement of AIDS research, such as, the addition of a flow cytometer; the first unit for determining CD4 status of HIV patients; assisting community based private organizations and the municipality of Ponce in obtaining Ryan White CARE grants and a survey grant to conduct a migration/movement analysis of HIV patients; and an investigation of the molecular epidemiology of tuberculosis.

Researchers at the Ponce School of Medicine are investigating drug abuse effects which may render the placenta more prone to HIV transmission during parturition. They have shown that all antibodies are not equally transferred from the placenta and the amount of maternal antibodies transferred is not solely determined by the maternal titer.

Vaccine studies at NCRR resources are determining the safety, tolerance, and immunogenicity of recombinant vaccines in HIV-1. Primary endpoints are stabilization or reduction in the rate of decline of CD4 cell counts, decline in the incidence of clinical HIV-related events, and a decrease in viral burden in the immunized group.

An NCRR supported investigator has developed an experimental vaccine against an AIDS-like infection of monkeys caused by SIV, the simian immunodeficiency virus. The nef gene, one of the virus's nine genes, was deleted and the vaccine has completely protected monkeys against SIV disease for more than three years, the strongest and longest lasting of any AIDS-related experimental vaccine. The possibility of a nef-deleted mutant gene in viruses from long-term non-progressors to AIDS is being studied.

Longitudinal magnetic resonance spectroscopy (MRS) provides a means of tracking the time course of alterations in CNS metabolic measurements. Two recent studies have identified indications of the progression of HIV to AIDS before any other manifestation of the disease: visualization of alterations in the brain of asymptomatic HIV seropositive subjects and identification of a product of HIV gene expression which may play a major role in the replication of the virus and its spread. These studies should provide a metabolic basis for "staging" the degree of CNS involvement.

A major recent advance in breast cancer research is the identification of the breast cancer susceptibility gene, BRCA1, and narrowing the search for a second, BRCA2. Science, the publication reporting this finding, cited support from NCRR resources where the kindreds reported in this landmark paper were evaluated and continue to be studied. The resource was also involved in generating the cell lines from which the DNA was extracted for the mutational analysis. Identification of BRCA1 should facilitate early diagnosis of breast and ovarian cancer among a subset of individuals genetically prone to those cancers through the BRCA1 and related gene. A followup study is investigating the psychological impact of being identified as having a BRCA1 mutation and being genetically susceptible to the development of breast cancer.

The BRCA2 region and the estrogen receptor region are being investigated in a panel of Louisiana families with known BRCA1 linkage. This research at a Human Genetic Analysis Resource will use these BRCA2-linked families to try to narrow the area on a chromosome which contains this gene.

Between ten and thirty percent of women who have breast cancer and undergo mammography have negative mammograms. In order to increase the efficiency and effectiveness of mammography screening procedures, NCRR is supporting development of computer-vision schemes to detect masses and microcalcifications in digital mammograms. Preliminary research includes development of automated detection of cluster microcalcifications and mammographic masses, application of artificial networks to mammographic interpretation, and development of automated characterization of mammographic lesions.

Knowledge of the atomic structure of NB-1, a small protein absent in all breast tumor cell lines tested so far, would enable investigators to study the link between the absence of NB-1 in malignant breast cells and the abnormal differentiation patterns. Investigators at a Synchrotron Radiation Resource have begun preliminary protein crystallography of NB-1.

Development of cell lines for investigating mechanisms which control breast tumor cell metastasis and invasion is being investigated at a National Flow Cytometry and Sorting Research Resource by applying flow cytometric methods.

The oncogene, neu/her-2, is over-expressed in about 30 percent of human breast carcinomas and is clinically associated with poor prognosis. Recently, investigators at a Biomedical Complex Carbohydrates resource have demonstrated a link between the activity of neu/her-2 and cell surface oligosaccharide expression by showing that over-expression of this oncogene causes a specific increase in GlcNAc-T V activity and message levels. The cells over-expressing this oncogene are tumorigenic, metastatic, and display altered cell adhesion. This research will help to define precisely the structural changes caused on cell surfaces.

Progestins, as well as estrogen, have been found to stimulate the growth of a human cancer cell line (T47D), contrary to previous experiments. Further research showed that a combined antiestrogen/antiprogestin treatment was more effective than antiestrogen alone at inhibiting the cancer cell growth. Also, progestin stimulated growth associated changes in breast cancer cells have been visualized by transmission and scanning electron microscopes.

DNA oxidative damage is suspected to be a factor in diseases associated with aging such as cancer. NCRR-supported researchers found that women at high risk for breast cancer who adhered to a low-fat diet had less DNA oxidative damage than did high risk women who remained on regular diets.

ALZHEIMER'S DISEASE

Mr. Stokes: I understand that researchers supported by the General Clinical Research Centers have reported a link between the risk of Alzheimer's Disease and ethnic background. What is the significance of this finding?

Dr. Vaitukaitis: In the search to define risk factors for Alzheimer's disease, scientists have identified a family of genes called Apo-E genes which are the same genes that are associated with risk of heart attack. Several research groups have shown that members of Alzheimer's-prone families who have the Apo-E gene called ϵ-4 -- one of the forms of the Apo-E gene -- face a greater risk of getting Alzheimer's disease then members who have the ϵ-2 or ϵ-3 forms.

To learn if particular Apo-E genes make people of certain ethnic backgrounds more likely to develop Alzheimer's disease, researchers at Columbia University performed a case-control study that drew on the resources of the NCRR-supported General Clinical Research Center. The researchers compared the distribution of the three forms of the Apo-E gene among 145 Alzheimer's patients and a control group comprising 206 healthy unrelated individuals of African American, Hispanic, and Caucasian descent. Both groups contained an almost even representation of men and women--46 to 96 years old--and of the three ethnic groups.

As in previous studies, people who had the ϵ-4 gene had a high risk of being afflicted by Alzheimer's disease. If they had inherited the gene from both parents, their risk was five times higher than the risk of people who had other genes. But the risk diminished for African Americans more than 70 years old. Within this group, approximately equal numbers of patients and controls carried ϵ-4.

The researchers also found that although the ϵ-2 form seemed to protect Caucasians, it posed eight times the disease risk for African Americans and was an apparent liability among Hispanics more than 70 years old. In the latter two groups, more Alzheimer's patients than healthy people carried the ϵ-2 gene. The reverse was true for Caucasians.

There could be several explanations for the ethnic diversity in disease risk. The researchers caution that the results are preliminary and based on relatively small numbers of individuals from the different ethnic groups. Testing for Apo-E cannot predict who will develop Alzheimer's disease. These genetic risk factors must be studied further. In a planned prospective trial, the researchers will follow groups of healthy people who carry different types of Apo-E genes and watch for those who develop Alzheimer's disease. It will be important to include different ethnic groups in the study since it is not clear that the Apo-E connection accounts for Alzheimer's disease in all populations.

DIABETES

Mr. Stokes: As you may know, nearly 14 million Americans suffer from Diabetes and nearly half of them are not even aware that they have the disease. What is the Center's role in the NIH's Diabetes research activities?

Dr. Vaitukaitis: Investigators conducted a study to determine whether the severity of hepatic and extrahepatic insulin resistance were comparable and whether the effectiveness of glucose per se was impaired in the presence of continuously changing insulin and glucose concentrations in Non-Insulin-Dependent Diabetes Mellitus (NIDDM). The study demonstrated a discordance between the severity of hepatic and extrahepatic insulin resistance in people with NIDDM. Although restoration of insulin secretion in people with NIDDM may be accompanied by a normal hepatic response, extrahepatic carbohydrate metabolism is likely to remain abnormal. This study suggests that new therapies should be directed primarily toward improvement of extrahepatic insulin action rather than altering hepatic responsiveness to insulin or glucose effectiveness.

Investigators performed oral and intravenous glucose-tolerance tests, studies with the euglycemic-hyperinsulinemic clamp, meal-tolerance tests and 24-hour blood-pressure measurements at base line and after the administration of troglitazone. The study showed that troglitazone decreases insulin resistance and improves glucose tolerance in obese subjects with either impaired or normal glucose tolerance.

Insulin-dependent diabetes mellitus (IDDM) is a T-cell-mediated autoimmune disease of unknown origin. The onset of the disease is thought to be triggered by environmental factors that result in the destruction of pancreatic islet B-cells in genetically predisposed individuals. Researchers hypothesize that the pancreatic insulin-producing islet cells express a membrane-bound superantigen that may be the factor that triggers this tissue-specific autoimmune disease. Although further studies must be done to identify and characterize this putative superantigen, this study may lead to the determination that exposure to superantigens is the triggering event in the onset of IDDM.

NCRR provides support in the identification and development of vertebrate animal models for human diseases that are essential for biomedical research. A recent study showed how an acute onset of diabetes of only two weeks duration is associated with alterations in cerebral blood flow physiology, specifically CO_2 reactivity. Additionally, another study demonstrated that moderate dietary restriction will slow the rate of functional aging as assessed in rhesus monkeys by body size and composition, glucose tolerance and insulin sensitivity, energy expenditure, immunological function and visual accommodation.

Using an NCRR-supported Mass Spectrometry Resource investigators have conducted experiments to assess the role of sorbitol dehydrogenase in mediating neural and vascular dysfunction in rats with streptozotocin-induced diabetes. Observations suggest that inhibition of sorbitol dehydrogenase may represent a potentially useful therapeutic intervention in the prevention of these complications of diabetes mellitus.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes: In response to congressional concern for developing the Clinical Research Infrastructure at minority institutions, NIH indicated that plans were underway to address this concern through a collaborative effort between the RCMI and GCRC Programs. Where are you in this planning process? Since the FY 1996 budget request for the RCMI Program is essentially the same as the FY 1995 appropriations, how do you intend to address this congressional concern with the proposed budget?

Dr. Vaitukaitis: The two-year collaborative planning process for developing clinical research infrastructure at minority institutions, as described previously, has been completed; NCRR expects to support three to four programs at up to $600,000 per year direct costs, for five years, beginning in FY 1995. Collaboration between the RCMI eligible minority institutions and GCRC grantees is being encouraged. We anticipate that the increase in the RCMI Program budget for FY 1995 and 1996 should be adequate to meet this high priority RCMI Program need.

Mr. Stokes: How does the budget increase proposed for the RCMI Program compare with the FY 1995 budget request for the National Center for Research Resources (NCRR)? How will the unmet needs of the RCMI Program be addressed in the FY 1996 NCRR budget? Will this budget be sufficient to insure that this Program can meet its objectives?

Dr. Vaitukaitis: A 1.0 percent increase in the RCMI Program budget has been requested for FY 1996. For NCRR, the overall requested increase of 7.4 percent reflects several special emphasis areas, including high performance computing, gene therapy, and breast cancer. Also included is a request for expansion of research facility construction. These are examples of critically important areas for the NCRR mission, and areas where alternative funding sources are often not available or otherwise very limited.

Although the RCMI Program also develops new initiatives that are equally critical for NCRR, a unique aspect of this process in RCMI is that other NIH institutes, centers or offices are often involved in the planning and development phase. As the goals and objectives evolve, they frequently turn out to be of mutual interest, resulting in a collaborative effort that provides additional resources, including financial resources, needed for expansion, without requiring substantial additional budget increases to implement the initiative.

Mr. Stokes: I believe the RCMI Program has had a major impact in facilitating the participation of doctoral degree granting minority institutions in NIH-supported programs. Are there plans to design a similar program for minority institutions that do not award doctoral degrees?

Dr. Vaitukaitis: The NCRR has embarked on a collaborative effort with the Office for Research on Minority Health (ORMH), NIH to develop a special initiative, "Research Infrastructure in Minority Institutions (RIMI)" for minority institutions granting masters degrees in the health fields (and some baccalaureate degree granting minority institutions), to develop their health-related research infrastructure. An important feature of the RIMI Program is the requirement for collaborative ties to biomedically research-intensive doctoral degree granting institutions. This new initiative is intended not only to facilitate the participation of these minority institutions in NIH programs, but also to provide an additional pathway for minority students to enter the health sciences and to benefit from an enhanced biomedical research environment while attending these minority institutions. NCRR expects to award up to 20 one year planning grants for up to $50,000 direct costs each in FY 1995.

Mr. Stokes: To what extent has there been cooperation between the Office of Research on Minority Health (ORMH) and NCRR in achieving common objectives?

Dr. Vaitukaitis: Collaborative interaction between the ORMH and the NCRR has been steadily increasing for many years. An excellent example is the RIMI initiative described above, wherein ORMH has agreed to provide financial support for both planning and implementation grants, and NCRR has agreed to provide program management. The ORMH has previously supported RCMI infrastructure in environmental health (up to $1.5 million per year), and has provided about $500,000 in each of the past three years for the minority high school initiative. In addition, ORMH contributed over $1.0 million to the Research Facility Improvement Program for construction needs at minority institutions in FY 1994. Support has been provided for other NCRR activities as well, such as MCAP. We anticipate that the cooperation and collaboration between NCRR and ORMH will continue in areas of mutual interest.

Mr. Stokes: The congressional intent in providing funds for the Facilities Construction Program was to ensure that the needs of institutions of emerging excellence, i.e., the RCMI programs, be addressed. Therefore, I am interested in knowing which RCMI-eligible institutions received awards in FY 1994? Provide for the record the name of the institutions receiving awards in 1994 and the amount of each.

Dr. Vaitukaitis: Two extramural construction grant awards were made to RCMI grantee institutions in FY 1994. Meharry Medical College was awarded $1,007,683 to repair structural flaws in a basic science research center, and Morehouse School of Medicine was awarded $1,750,000 for construction and renovation of space for clinical research, development of a neuroscience center and expansion of a laboratory animal care center. In both cases, the ORMH shared in the funding of these applications.

CLINICAL RESEARCH

Ms. Lowey: I strongly support your work -- clinical research and training of physicians is so important to translate the important research discoveries to the improvement of treatments for patients of the diseases NIH studies.

I spoke with Dr. Varmus about some of my concerns -- particularly the Division of Research Grants (DRG) report that suggested that in some cases patient-oriented research fares less well than laboratory research in the grants process. I have some additional questions.

As you state in your testimony -- and as I also discussed with Dr. Varmus -- the Institute of Medicine (IOM) issued a compelling report last September on Careers in Clinical Research. The report sounded an alarm about the loss of physicians from the ranks of our Nation's researchers and highlighted particularly the difficulties physicians have training for and pursuing careers in patient-oriented research.

The report offered some specific recommendations as to steps that NIH could take to enhance the environment for clinical research and clinical research training. What has the NCRR done to date to examine and implement the IOM recommendations?

Dr. Vaitukaitis: The NCRR, in consultation with our National Advisory Council, has carefully reviewed options for expanding the availability of the Clinical Associate Physician (CAP) and Minority Associate Physician (MCAP) awards to institutions with GCRCs and has made changes in the guidelines for these programs to enhance the number of awards. In addition, the NCRR has established a new award called the Clinical Research Scholars Program (CRSP) to enable clinical investigators to concentrate for one year on curriculum based studies such as clinical research design, bioethics, biostatistics, and epidemiology which, in some instances, could lead to an advanced degree. All of these initiatives will encourage and support physicians and dentists to further their careers in clinical research and enable them to become independent clinical research scientists and investigators in the future.

Ms. Lowey: The report also recommends the creation of a national body to monitor clinical research and training needs and make recommendations to Congress and the academic community. How do you believe such an advisory group should be structured and funded and where should it be housed?

Dr. Vaitukaitis: A national advisory group should encompass all of clinical research. Clinical research is an important component of the scientific endeavor of all institutes and centers at the NIH. The intramural clinical research is carried out at the Warren Grant Magnuson Clinical Center. Extramural clinical research is performed at the General Clinical Research Centers located at 75 geographically dispersed academic institutions as well as in specialized clinical centers supported by the Institutes and Centers. Besides NIH-supported clinical research, considerable work in clinical research and clinical trials is carried out by industry or privately supported organizations. Therefore, to encompass all of the parties participating in and interacting in the clinical research, the committee should be structured to have broad representation from the NIH and non-NIH participants.

Ms. Lowey: I know you share my concern about the National Academy of Sciences study released last year revealing a 54 percent decline between 1985 and 1993 in the number of individuals aged 36 and under applying to NIH for support. It seems to me from the IOM and DRG analyses that this problem may be more acute among physicians.

Has NCRR asked the Academy to analyze M.D.s and Ph.D.s separately in its follow-up study, to determine if the problem is more acute among physicians? Would you consider doing so?

Dr. Vaitukaitis: NCRR is very concerned as are the other components of NIH about fewer M.D.s and Ph.D.s selecting biomedical research careers. We do know that the average age for M.D.s and Ph.D.s is increasing in general. To what extent that is contributing to the apparent decline in young individuals, aged 36 and under, applying for NIH research grants is unknown. NCRR has begun examining the relative impact on M.D.s versus Ph.D.s and will continue that analysis in conjunction with the Office of the NIH Director and DRG.

GENERAL CLINICAL RESEARCH CENTERS

Ms. Lowey: Both the DRG and IOM reports focus on the General Clinical Research Centers (GCRC) Program of the NCRR as an important site for high quality patient-oriented research. Given the cost-containment pressures we have just discussed, these Centers are becoming far more important and should be enhanced and expanded.

What steps is NCRR taking to strengthen the GCRC Program?

Dr. Vaitukaitis: The NCRR has taken several steps to strengthen the GCRC Program. To enhance the availability of clinically applicable gene vectors for human studies, the NCRR will cosupport National Gene Vector Laboratories. These Gene Vector Laboratories will allow investigators with RAC approved vectors to have human grade vectors produced, safety tested, and distributed without additional cost. NCRR also has initiated a program to upgrade existing GCRC core facilities to accommodate a new field of experimentation in cellular therapies. The GCRC Program will increase clinical research training by accommodating more physicians and dentists who can apply for support through the Clinical Associate Physician and Minority Clinical Associate Physician Awards. The GCRC program is also initiating the Clinical Research Scholar Program (CRSP) for physicians and dentists interested in one year of dedicated curriculum based studies to prepare them for further clinical studies and careers in clinical investigation.

Ms. Lowey: A 1993 panel report recommended that the NIH Director's office develop mechanisms to insure the expanded involvement of all NIH institutes in maximum use of GCRCs. Has this been done?

Dr. Vaitukaitis: The General Clinical Research Centers provide the infrastructure (hospital inpatient and outpatient facilities, trained research nursing, bionutritionists, computer systems and systems managers, biostatisticians and a variety of core laboratory services) to facilitate the work of NIH funded investigators who receive their funding from all NIH Institutes and Centers. In one instance, a GCRC is cofunded with the National Institute on Aging. The GCRC program staff tracks each RFA announcement from all Institutes and Centers to insure that the categorical institutes are aware of NCRR's willingness to support clinical studies, should such facilities be required. The GCRC Program Director and staff participate in all of the Task Forces or multi-institute advisory groups pertaining to clinical research.

Ms. Lowey: That same report recommended the development of a national clinical research agenda. Have you made progress in this area?

Dr. Vaitukaitis: NCRR, in concert with the research community, will be updating its Strategic Plan. Clinical research is a central focus of that plan as well as the pivotal role GCRCs play in facilitating clinical research. As a result of recommendations developed in conjunction with the academic research community, NCRR expanded its programs for career development for patient oriented research, modified the role of GCRC core laboratories so that they provide shared resources for multi-disciplinary research, initiated development of National Gene Vector Laboratories and have initiated workshops and curricula for clinical research at GCRC sites.

Ms. Lowey: The report also recommended a number of new initiatives: a debt forgiveness program for clinical research trainees in the GCRCs, some changes in the rules governing training awards for young physician scientists, a new program for the re-training of mature clinician scientists. What progress has been made on these recommendations?

Dr. Vaitukaitis: No debt forgiveness program for clinical research trainees exists in the academic research community. However, one does exist for disadvantaged physicians for the NIH intramural program, and NCRR is reviewing the potential of such a mechanism. NCRR has also considered a re-entry career development program for mature clinical scientists but deferred its implementation because of other higher priorities.

CLINICAL RESEARCH OMBUDSMAN

Ms. Lowey: When Dr. Varmus testified, he mentioned that he had recently appointed Dr. Laurence Shulman as the Ombudsman for clinical research. He is a terrific choice, and I am pleased Dr. Varmus made this appointment.

How do you see him operating in this new role? Will he be able to make up for the lost time?

Dr. Vaitukaitis: I have met with Dr. Shulman since he assumed his new responsibilities related to clinical research. We have exchanged ideas and information and discussed problems encountered by patient-oriented investigators. We plan to continue to meet and exchange information. Dr. Shulman's enthusiasm for and knowledge of clinical research are assets that will serve the clinically-based biomedical research community well.

ACADEMIC HEALTH CENTERS AND MANAGED CARE

Ms. Lowey: The lay and medical press are focussing considerable attention on the problems academic health centers have in the current environment where managed care is expanding rapidly. A recent Federal study concluded that managed care plans are not willing to accommodate financially the special needs and problems of these centers.

Has the NCRR attempted to quantify the impact that competition is having on the research programs of our Nation's medical centers?

Dr. Vaitukaitis: NCRR has initially surveyed its network of GCRCs to ascertain the impact of managed care on clinical research. In those geographic areas in which managed care has penetrated significantly, patient referrals for clinical research projects has been negatively impacted. Some managed care organizations (MCOs) are refusing to allow their patients to participate as clinical research subjects. Other MCOs allow their patients to participate. Much more work needs to be done to define the breadth and depth of the impact of MCOs on clinical research. We are in the process of doing that.

Ms. Lowey: With so much of NIH's mission being carried out in these centers, shouldn't the NIH play a leadership role in analyzing this situation and making recommendations as to how we can protect the research efforts of our academic centers?

Dr. Vaitukaitis: On behalf of NIH and in conjunction with the Office of the Assistant Secretary for Health, I am working with a contractor knowledgeable in managed care and related issues to develop an approach, in concert with broad representation for academic health centers, clinical investigators, MCOs and NIH program staff. As a result of this interaction, recommendations will be developed to assure patient access for clinical research at academic health centers.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

FY 1996 Budget — Page No.

Organization chart.......... 134

Appropriation language.......... 135

Amounts available for obligation.......... 137

Budget mechanism table.......... 138

Summary of changes.......... 140

Budget authority by object.......... 141

Administrative costs.......... 143

Authorizing legislation.......... 144

Appropriation history.......... 145

Budget authority by activity.......... 147

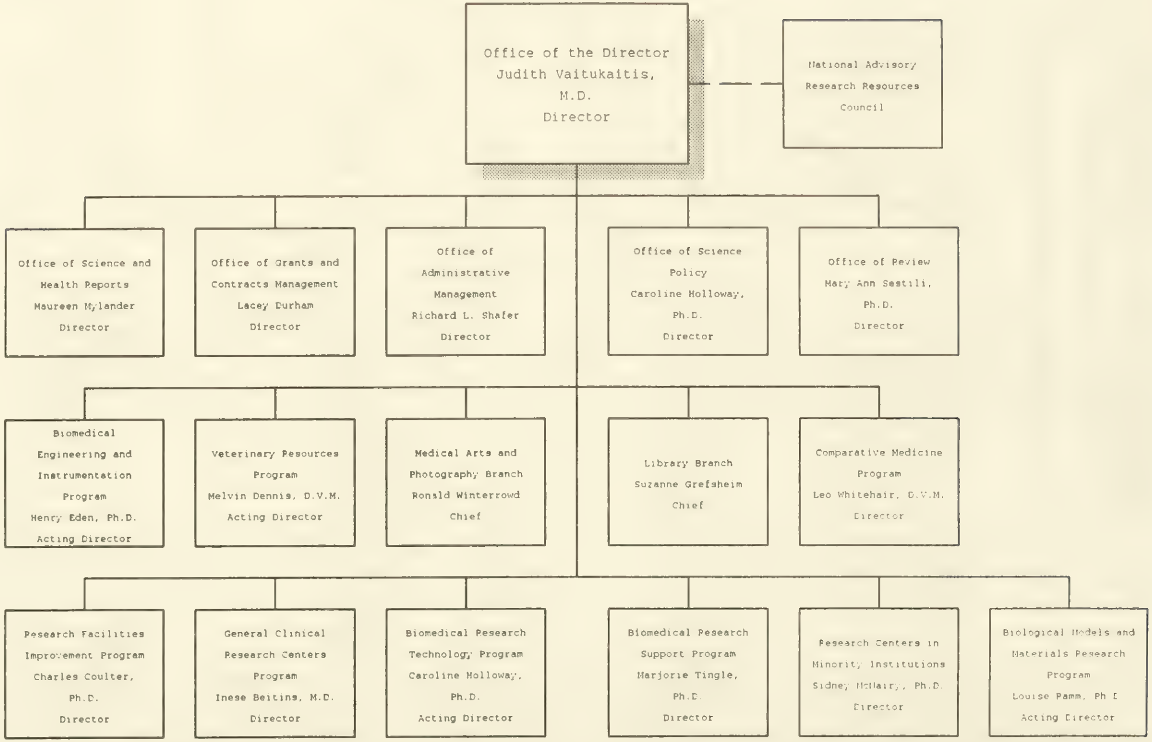
Justification:

A. General Statement.......... 149
B. Extramural research.......... 152
C. Research management and support.......... 161
D. Detail of full-time equivalent employment (FTE).......... 162
E. Detail of end-of-year employment.......... 163

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

For carrying out section 301 and title IV of the Public Health Service Act with respect to research resources and general research support grants, [$294,877,000] *$316,544,000*: Provided, That none of these funds shall be used to pay recipients of the general research support grants program any amount for indirect expenses in connection with such grants: Provided further, That $20,000,000 shall be for extramural construction grants.

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Amounts Available for Obligation 1/

	1994 Actual 2/	1995 Appropriation	1995 Current Estimate	1996 Estimate
Appropriation..........	$331,915,000	$294,877,000	$294,877,000	$316,544,000
Proposed Rescission....			-1,000,000	
Section 205 Procurement reduction............	---	-57,000	-57,000	---
Section 207 Rent reduction............	---	-23,000	-23,000	---
Section 513 S&E reduction............	---	-60,000	-60,000	---
Subtotal, adjusted appropriation......	331,915,000	294,737,000	293,737,000	316,544,000
Comparable transfer to the Office of AIDS Research NIH for HIV Activities...........	-61,383,000	---	---	---
Subtotal, adjusted budget authority...	270,532,000	294,737,000	293,737,000	316,544,000
Unobligated balance, lapsing.............	-13,000	---	---	---
Total, obligations...	270,519,000	294,737,000	293,737,000	316,544,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994 -- $8,235,000; and FY 1995 -- $8,469,000; and FY 1996 -- $8,590,000.

Also excludes funding for HIV activities: FY 1995 -- $64,630,000; FY 1996 -- $68,370,000, included in the Office of AIDS Research, NIH.

2/ Excludes an emergency supplemental of $1,000,000 transferred from OASH for earthquake relief.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Mechanism

	1994 Actual 1/		1995 Appropriation		1995 Current Estimate		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research grants:								
Research projects:								
Noncompeting	50	$9,385,000	48	$9,095,000	48	$9,095,000	68	$13,380,000
Admin. suppl	(3)	28,000						
Competing								
Renewal	6	1,419,000	10	2,567,000	10	2,567,000	10	2,837,000
New	22	2,998,000	30	4,088,000	30	4,088,000	34	4,818,000
Supplemental	--	---	--	---	--	---	--	---
Subtotal competing	28	4,417,000	40	6,655,000	40	6,655,000	44	7,655,000
SBIR/STTR	31	4,183,000	50	5,985,000	50	5,985,000	70	8,436,000
Subtotal, res. proj	109	18,013,000	138	21,735,000	138	21,735,000	182	29,471,000
Research Centers:								
Clinical research	76	101,392,000	76	104,979,000	76	104,979,000	76	108,834,000
Biomedical research technology	62	43,978,000	62	45,168,000	62	45,168,000	62	46,688,000
Comparative medicine/biological models and materials	30	34,722,000	30	34,580,000	30	34,580,000	30	34,580,000
Research centers in minority institutions	19	20,915,000	19	22,285,000	19	22,285,000	19	22,285,000
Subtotal, research centers	187	201,007,000	187	207,012,000	187	207,012,000	187	212,387,000

1/ Excludes an emergency supplemental of $1,000,000 transferred from OASH for earthquake relief.

Other research:								
Research career programs..........	14	1,001,000	14	1,001,000	14	1,001,000	14	1,001,000
Biomedical research support.......	106	17,160,000	108	16,094,000	108	16,094,000	160	25,255,000
Other research related............	35	7,525,000	50	8,342,000	50	8,342,000	50	8,342,000
Subtotal, other research......	155	25,686,000	172	25,437,000	172	25,437,000	226	34,598,000
Total, research grants.............	451	244,706,000	497	254,184,000	497	254,184,000	595	276,456,000
Training:								
Individual awards:								
Noncompeting.....................	1	35,000	2	72,000	2	72,000	4	123,000
Competing........................	3	82,000	2	51,000	2	51,000	--	---
Subtotal, individual...............	4	117,000	4	123,000	4	123,000	4	123,000
Institutional awards:								
Noncompeting.....................	70	2,432,000	72	2,585,000	72	2,585,000	72	2,585,000
Competing........................	2	167,000	--	---	--	---	--	---
Subtotal, institutional............	72	2,599,000	72	2,585,000	72	2,585,000	72	2,585,000
Total, training....................	76	2,716,000	76	2,708,000	76	2,708,000	76	2,708,000
Research and development contracts..	11	3,802,000	11	3,731,000	11	3,731,000	7	3,076,000
(SBIR/STTR)......................	(5)	(455,000)	(4)	(454,000)	(4)	(454,000)	(--)	(---)
Construction........................		6,840,000		20,000,000		19,000,000		20,000,000
Research management and	FTEs		FTEs		FTEs		FTEs	
support..........................	98	12,468,000	100	14,114,000	100	14,114,000	98	14,304,000
Total..............................	98	270,532,000	100	294,737,000	100	293,737,000	98	316,544,000
Clinical Trials..................		(41,333,000)		(42,710,000)		(42,710,000)		(44,495,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Summary of Changes

1995 Estimated budget authority	$293,737,000
1996 Estimated budget authority	316,544,000
Net change	+22,807,000

	1995 Current Estimate Base		Change from Base	
	(FTEs)	Budget Authority	(FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Research Management & Support				
a. Within grade increases	---	$5,288,000	---	+$79,000
b. Annualization of 1995 pay raise	---	5,288,000	---	+49,000
c. One more day of pay	---	5,288,000	---	+20,000
d. 1996 pay increases	---	5,288,000	---	+112,000
e. Federal Employees Compensation Fund	---	28,000	---	+1,000
f. DHHS Working Capital Fund	---	123,000	---	-23,000
g. Payment for Centrally Furnished Services	---	5,280,000	---	-410,000
h. Service & Supply Fund	---	1,220,000	---	+35,000
i. Increased costs of supplies and materials	---	2,326,000	---	+68,000
Subtotal	---		---	-69,000
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	48	9,095,000	+20	+4,285,000
b. Competing	40	6,655,000	+4	+1,000,000
c. SBIR/STTR	50	5,985,000	+20	+2,451,000
Total	138	21,735,000	+44	+7,736,000
2. Research centers	187	207,012,000	---	+5,375,000
3. Other Research	172	25,437,000	+52	+9,161,000
4. Research Training	76	2,708,000	--	---
5. Research & Development Contracts	11	3,731,000	-4	-655,000
6. Facilities Construction		19,000,000		+1,000,000
	(FTEs)		(FTEs)	
7. Research Management and Support	100	14,114,000	-2	+259,000
Subtotal				+22,876,000
Total changes				+22,807,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Authority by Object

	1995 Appropriation	1995 Current Estimate	1996 Estimate	Increase or Decrease
Total compensable work years:				
Full-time equivalent employment	100	100	98	-2
Full-time equivalent of overtime and holiday hours	2	2	2	---
Average ES salary	$103,000	$103,000	$103,000	---
Average GM/GS grade	10.0	10.0	10.0	---
Average GM/GS salary	$41,826	$41,826	$42,746	+$920
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	77,607	77,607	77,607	---
Personnel compensation:				
Full-time permanent	$4,076,000	$4,076,000	$4,240,000	+$164,000
Other than full-time permanent	199,000	199,000	208,000	+9,000
Other personnel compensation	156,000	156,000	161,000	+5,000
Total, personnel compensation	4,431,000	4,431,000	4,609,000	+178,000
Personnel benefits	851,000	851,000	885,000	+34,000
Benefits for former personnel	6,000	6,000	6,000	---
Travel and transportation of persons	119,000	119,000	123,000	+4,000
Transportation of things	66,000	66,000	33,000	-33,000

	1995 Appropriation	1995 Current Estimate	1996 Estimate	Increase or Decrease
Rent, communications, and utilities..................	311,000	311,000	294,000	-17,000
Printing and reproduction....	153,000	153,000	161,000	+8,000
Other services:				
Consultant services........	20,000	20,000	25,000	+5,000
Other Services.............	456,000	456,000	408,000	-48,000
Purchase from Govt. Accts..	7,466,000	7,466,000	7,520,000	+54,000
R&D Contracts..............	3,731,000	3,731,000	3,076,000	-655,000
Supplies and materials.......	44,000	44,000	45,000	+1,000
Equipment....................	163,000	163,000	166,000	+3,000
Grants, subsidies & contributions..............	276,892,000	275,892,000	299,164,000	+23,272,000
Unemployment compensation & insurance..................	28,000	28,000	29,000	+1,000
Total......................	294,737,000	293,737,000	316,544,000	+22,807,000

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time Permanent (11.1)	$4,076,000	$4,240,000	+$164,000
Other than Full-time Permanent (11.3)	199,000	208,000	+9,000
Other Personnel Compensation (11.5)	156,000	161,000	+5,000
Total Personnel Compensation(11.9)	4,431,000	4,609,000	+178,000
Civilian Personnel Benefits	851,000	885,000	+34,000
Benefits to Former Personnel (13.0)	6,000	6,000	---
Travel (21.0)	119,000	123,000	+4,000
Transportation of Things (22.0)	66,000	33,000	-33,000
Communications, Utilities, and Miscellaneous Charges (23.3)	311,000	294,000	-17,000
Printing and Reproduction (24.0)	153,000	161,000	+8,000
Consulting Services (25.1)	20,000	25,000	+5,000
Other Services (25.2)	456,000	408,000	-48,000
Purchases from Govt. Accts. (25.3)	4,986,000	5,069,000	+83,000
Operation of GOCOs (25.4)	---	---	---
Supplies and Materials (26.0)	44,000	45,000	+1,000
Total	11,443,000	11,658,000	+215,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Current Estimate	1996 Amount Authorized	1996 Budget Request
Research and Investigation...	Section 301	42s241	Indefinite	$291,029,000	Indefinite	$313,836,000
National Center for Research Resources..................	Section 479,480	42s287 287a,300a, and 5s332	Such sums as necessary		Such sums as necessary	
National Research Service Awards....................	Section 487	42s288	Such sums as necessary	2,708,000	Such sums as necessary	2,708,000
Total Budget Authority.....				293,737,000		316,544,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987 2/	$234,192,000	$317,826,000	$319,924,000	$322,860,000
1988	280,415,000	346,652,000 3/	367,415,000	368,153,000
1989	319,977,000 4/	355,767,000 5/	367,987,000	358,608,000 6/
1990	263,313,000 7/	356,128,000	362,253,000	353,734,000 8/
1991	319,151,000	355,962,000	331,629,000	335,255,000 9/
1991 Sequester				-4,000
1992	320,975,000	309,200,000	317,227,000	314,213,000 10/
1993	330,231,000	311,207,000	315,551,000	312,468,000 11/
1994	327,887,000	328,915,000	332,915,000	331,915,000
1995 12/	286,394,000	294,824,000	294,824,000	294,737,000 13/
1995 Rescission	-1,000,000			
1996 12/	316,544,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread funding among the institutes, including $6,142,000 for the Division of Research Resources.

3/ Does not include funding for AIDS research which was consolidated at the Secretary's level.

4/ The 1989 request excludes funds for AIDS research and education ($38,010,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $2,220,000 in NRSA training programs not considered.

6/ Reflects a 1.2% reduction ($4,356,000) and a reduction of $23,000 as a result of improved procurement practices from the appropriated level of $362,987,000 as required by P.L. 100-436 Sections 517 and 215 respectively.

7/ The 1990 request excludes funds for the National HIV program ($44,643,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

8/ Excludes enacted administrative reductions of $16,000 for procurement savings; $344,000 for extramural salary cap and $97,000 for salaries and expenses.

9/ Excludes enacted administrative reduction of $8,541,000.

10/ Includes enacted administration reduction of $669,000, and enacted recision of $338,000.

11/ Reflects a .8% reduction ($2,522,000), a S&E reduction ($235,000), and Consultant Services reduction ($26,000).

12/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995.

13/ Excludes enacted administrative reductions of $57,000, $23,000 and $60,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual 1/		1995 Current Estimate		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Shared resources...	--	$212,850	--	$211,389	--	$215,683	--	$224,168	--	$246,624	--	+$22,456
Infrastructure improvement......	--	29,664	--	28,618	--	32,802	--	46,202	--	47,202	--	+1,000
Human resource development......	--	8,852	--	8,846	--	9,578	--	9,253	--	8,414	--	-839
Subtotal, extramural.....	--	251,366	--	248,853	--	258,063	--	279,623	--	302,240	--	+22,617
Research management and support......	109	12,781	108	12,901	98	12,456	100	14,114	98	14,304	-2	+190
Subtotal, obligations....	109	264,147	108	261,754	98	270,519	100	293,737	98	316,544	-2	+22,807
Unobligated balance lapsing..........	--	+15	--	+22	--	+13	--	---	--	---	--	---
Total, budget authority......	109	264,162	108	261,776	98	270,532	100	293,737	98	316,544	-2	+22,807

1/ Excludes an emergency supplemental of $1,000,000 transferred from OASH for earthquake relief.

Note: Includes FTEs associated with HIV activities. Funds to support these activities are included in the NIH Office of AIDS Research.

Justification

National Center for Research Resources

FY 1994 Actual		FY 1995 Current Estimate		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
98	$270,532,000	100	$293,737,000	98	$316,544,000	-2	+$22,807,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Center for Research Resources. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The National Center for Research Resources (NCRR) serves as a "catalyst for discovery" by creating and providing critical research technologies and shared resources. This infrastructure underpins biomedical research and enables advances that improve the health of our Nation's citizens.

Biomedical research investigators supported by the Institutes and Centers of the National Institutes of Health require a broad array of technologies, tools and materials critical to their research efforts. From the models required for research on diseases and disabilities, to the biomedical technology and instrumentation necessary to elucidate cellular and molecular structure, to the clinical settings in which to conduct studies to discern the cause of disease and in which novel clinical trials of new therapies can be developed, biomedical researchers must have access to the necessary resources in order to continue to make progress against human disease and disability.

The NCRR has a unique mission at the National Institutes of Health: to develop critical research technologies and to provide cost-effective, multidisciplinary resources to biomedical investigators across the spectrum of research activities supported by the NIH. This mission has four major facets:

(1) Create resources and develop technologies that are cost-effective, accessible and responsive to the research needs of the biomedical research community. To meet these needs the NCRR must be in the vanguard of evolving trends in basic and clinical research so that resources will be available to facilitate that research.

(2) Provide shared clinical, primate and biotechnology resources for use by investigators supported by all the NIH Institutes and Centers. These resources, primarily centers, serve more than 7,000 researchers, supported through well over $1 billion of categorical Institute funds, thus leveraging those funds for more cost-effective and efficient research.

(3) Develop quick, flexible approaches to new and emerging biomedical research needs and opportunities. These innovations often involve high-risk research, but the payoffs may be invaluable.

(4) Strengthen the nation's biomedical research infrastructure through programs to develop and enhance the capacity of minority institutions and centers of emerging excellence to participate in biomedical research, to increase the exposure of K-12 students and their teachers to the life sciences, to improve the condition of research animal facilities, and to construct or renovate facilities for biomedical and behavioral research.

The NCRR plays a key role in addressing pressing trans-NIH research issues, such as access to state-of-the-art instrumentation and biotechnologies; containment of the escalating costs of highly sophisticated clinical research; development of appropriate, specialized research models both animal and nonanimal; and remedying the shortage of independent clinical investigators and the underrepresentation of minority investigators. Present and future program directions emphasize "smart," network-connected technologies, computer-aided drug design, development and testing of gene and molecular therapies, bioengineering approaches to decrease health care costs, and enhanced training and career development for patient-oriented research.

The President's appropriation request of $316,544,000 represents current law requirements. No proposed law amounts are included. Funding for the National Center for Research Resources for the last five years is as follows:

	Amount	FTEs
FY 1991	$288,377,000	103
FY 1992	264,162,000	109
FY 1993	261,776,000	108
FY 1994	270,532,000	98
FY 1995	293,737,000	100

Purpose and Method of Operation

The National Center for Research Resources funds the development, support and provision of shared research resources and technologies, as well as the enhancement of research capacity, through its extramural programs. Most of these crosscut the entire range of the Center's mission, utilizing a variety of funding mechanisms for institutional and investigator support. Resource centers constitute the largest proportion of the Center's budget, and support nationwide networks of centers for conducting cost-effective clinical research, for accessing state-of-the-art biomedical research technologies, and for conducting research in nonhuman primates and other animal or nonanimal models. The centers mechanisms is also utilized to help enhance the research capacity of minority institutions throughout the U.S. Research project grants and resource-related research grants support innovative development of technologies, including animals and other models, as well as those related to biotechnology. Through other support mechanisms, NCRR provides state-of-the-art instruments to be shared by several NIH-supported researchers, as well as an array of biological materials for use by investigators. NCRR also funds improvement of animal facilities, career development, and programs to encourage careers in science for underrepresented groups. NCRR provides training for research veterinarians and young clinical investigators, including minorities. Research contracts provide a variety of resources to individual investigators. The construction program provides for modernization of institutional research facilities.

Overall Budget Policy

The FY 1996 budget request for the National Center for Research Resources is $316,544,000, an increase of $22,807,000 over the FY 1995 current estimate of $293,737,000. Funding will be provided for high performance computing, gene therapy, breast cancer research initiatives, and shared instrumentation.

In FY 1996, the NCRR will support 68 noncompeting research project grants (RPGs) and 44 new or competing RPGs. The FY 1996 request will support 182 total research project grants at $29,471,000, an increase of 44 awards and $7,736,000 over the FY 1995 appropriation. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompetitive component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one-time non-recurring costs such as equipment. The growth in the average cost of competing grants from FY 1995 to FY 1996 by 4.6 percent exceeds the Biomedical Research and Development Price Index for NCRR because of the change in the mix of the types of grants and the science funded. The NCRR expects to fund more program projects, and new bioengineering grants will be more expensive than the average grant supported in FY 1995.

The NCRR will support 187 research resource centers, with an increase of $5,375,000 over the FY 1995 level. NCRR will maintain support to 76 general clinical research centers, 62 biomedical research technology centers, 7 regional primate research centers, 17 laboratory animal sciences centers, 6 biological models and materials research centers, and 19 research centers in minority institutions.

In the "Other Research" category, the shared instrumentation grants program will receive an increase of $10,000,000, more than doubling the amount available for the program in FY 1995, for a total level of $18,841,000. The minority high school student research apprentice activity has been phased out and replaced with a competitive minority initiative for K-12 teachers and high school students, which will be funded at a level of $6,414,000. Approximately 20 science education partnership awards will be funded, at a level of $2,000,000, and about 13 institutional development awards will be made for a total of $1,100,000. Approximately 14 research career awards will be made, and there will be approximately 19 other research-related awards.

The FY 1996 request for research training is $2,708,000, the same as the FY 1995 level, and will support approximately 72 institutional full-time equivalent training positions, and four individual fellowships. The budget request for research and development contracts is $3,076,000, a reduction of $655,000 as compared to $3,731,000 in FY 1995, supporting seven contracts. The FY 1996 request for research facilities construction is $20,000,000, an increase of $1,000,000 over the FY 1995 current estimate of $19,000,000.

The FY 1996 budget request for Research Management and Support is $14,304,000, an increase of $190,000 or 1.3 percent over FY 1995. Approximately 98 FTEs will be supported, two fewer than in FY 1995.

National Center for Research Resources

Extramural Research

Authorizing Legislation - Sections 301, 479, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Current Estimate	FY 1996 Estimate	Increase or Decrease
$258,064,000	$279,623,000	$302,240,000	+$22,617,000

The Extramural Research Programs of the National Center for Research Resources are NIH's focal point for cost-saving, shared research resources and technologies that catalyze discoveries leading to improving human health. These Programs benefit all of NIH. They include national networks of resources that: (1) foster clinical research in an array of diseases in children and adults; (2) speed the development of sophisticated instrumentation and biotechnologies; and (3) provide key models and materials, including animal models, for studies of disease. NCRR's extramural programs also (4) expand the participation of underrepresented groups in biomedical research, including the development of the research capacity of minority institutions, and (5) support innovative science education.

NCRR's extramural programs are flexible in design. Innovative funding mechanisms ensure rapid response to unanticipated health research challenges across many scientific disciplines. In keeping with its response to vital health concerns in the past, NCRR proposes initiatives that will facilitate NIH-wide progress in biomedical research and discovery in the future.

Funding for NCRR's Extramural Programs during the last five years has been as follows:

	Amount
FY 1991	$275,904,000
FY 1992	251,366,000
FY 1993	248,853,000
FY 1994	258,064,000
FY 1995	279,623,000

Rationale for the Budget Request

The FY 1996 budget request for the non-AIDS extramural research activities of the NCRR is $302,240,000, an increase of 8.1 percent over the FY 1995 estimate of $279,623,000. Funds will be used to expand breast cancer research, high performance computing, human gene therapy, and shared instrumentation. The FY 1996 extramural request will provide funds to support the following activities: Shared Resources: $246,624,000, an increase of $22,456,000 or 9.1 percent over the FY 1995 estimate of $224,168,000; Infrastructure Improvement: $47,202,000, an increase of $1,000,000 over the

FY 1995 estimate of $46,202,000; Human Resources Development: $8,414,000, a decrease of $839,000 or 10 percent below the FY 1995 estimate of $9,253,000.

Shared Resources

The National Center for Research Resources serves as a catalyst for discovery for NIH-supported investigators throughout the Nation by creating, developing and providing a comprehensive range of human, animal, technological and shared resources to enable biomedical research advances. The NCRR promotes collaborations within and across scientific disciplines and provides quick, flexible approaches to new and emerging research needs. The collective networks of shared resources are accessed by more than 10,000 investigators annually.

Clinical research resources include a national network of General Clinical Research Centers (GCRCs) which provide clinical research infrastructure, usually at academic health centers where the results of bench research can be translated to new or improved therapies and prevention strategies for an array of diseases. The GCRCs also provide a setting for junior career development of physicians or dentists to become independent investigators for patient-oriented research. The GCRCs extend the range and intensity of clinical research by leveraging funding provided to investigators who study a broad range of diseases and disorders affecting children and adults. This cost-effective network leads to the development of new diagnostic tests, therapies and prevention strategies which mirror the research missions of all NIH components.

Biotechnology resources give the scientific community access to advanced technologies essential for biomedical research. NCRR-funded biotechnology centers serve as hubs for thousands of biomedical investigations throughout the country each year. These centers help offset rising health research costs by developing and providing state-of-the-art technologies that are too expensive or scarce for individual investigators to access at their own institutions. For example, biomedical computing has become critical to biomedical research, particularly in the areas of modeling and simulation, imaging and scientific visualization, decision support for biomedical research, as well as for molecular and cellular structure and function. Expert scientists and engineers staff these advanced biotechnology centers, and collaborate with biomedical scientists at other academic health centers, at universities and in industry, to develop and apply cutting-edge technologies to promising areas of biomedical research. Separately, the Shared Instrumentation Grant program provides sophisticated instruments--nuclear magnetic resonance spectrometers, mass spectrometers, protein and DNA sequencers--which, because of their high cost, are unlikely to be funded through other grant mechanisms. These instruments are shared by an average of approximately 11 NIH-supported investigators, thereby ensuring maximum return on investment.

Comparative medicine resources help meet the needs of biomedical investigators for appropriate animal and non-animal models for studies of human disease. One of the hallmarks of NCRR is its network of seven Regional Primate Research Centers, established in the early 1960's. NCRR also supports development of unique animal models, including transgenic and knock-out animal models as well as worms and marine animals, for research on a broad range of health problems, from AIDS, Alzheimer's, and other conditions of aging populations, to addiction to drugs of abuse.

Genetic Research

In the search to define the risk factors for Alzheimer's disease, scientists have located a family of genes called Apo-ε genes. These genes are the same ones associated with risk of heart attack. The genes encode blood-borne proteins, known as Apo-ε proteins, that ferry cholesterol and other types of fat from the gut, where fats are absorbed, to organs where fats are stored. Several research groups have shown that members of Alzheimer's-prone families who have the Apo-ε gene called ε-4, one of the rare forms of the Apo-ε gene, face a higher risk of Alzheimer's than members who had the ε-2 or ε-3 forms or alleles. Investigators compared the distribution of the ε-2, ε-3, and ε-4 forms of the Apo-ε gene among 145 Alzheimer's patients with that among a control group. If individuals inherited the ε4-gene from both parents, their risk was five times higher than normal. But that risk diminished for African-Americans more than 70 years old. However, since Apo-ε is neither sufficient nor necessary to cause heart disease or Alzheimer's disease, it may be part of a group of genes that predispose a person to these diseases.

Gene Therapy

Gene therapy is among the fastest growing and most promising areas of research, with unparalleled potential for preventing many common and rare diseases and disorders, and for reducing costs of health care in the future. NCRR's General Clinical Research Centers are the principal sites of much of the clinical genetic research ongoing in the U.S. for gene therapy of single- and multi-gene disorders. To quickly expand the capacity of clinical investigators to proceed with gene therapy, NCRR, together with other NIH Institutes, solicited applications, to be funded in fiscal year 1995, for National Gene Vector Laboratories. These shared resources will facilitate production of vehicles designed to deliver genetic material into human somatic cells for the prevention, treatment, and cure of a wide variety of medical conditions through human gene therapy -- for single gene disorders such as cystic fibrosis, immune deficiencies, hemoglobinopathies, hyperlipidemias and multifactorial disorders such as cancer, hypertension, diabetes, heart disease and pulmonary diseases. This important initiative will continue in FY 1996, and will also include studies of novel gene vectors in animal models. In addition, specially adapted cellular therapy laboratories will be established at GCRC sites to complement somatic gene therapies.

In FY 1996 the national network of National Gene Vector Laboratories will continue to be supported and developed in order to produce and distribute safe, high-quality vectors in sufficient quantities for rapid pursuit of promising gene therapy research. The network of GCRCs will facilitate a wide range of gene therapies for both inherited and acquired diseases.

Specific cells derived from patients with lymphomas, cancers, and autoimmune diseases can be separated, grown in culture and either transformed or manipulated to attain characteristics to eradicate or ameliorate a disease. For example, one may be able to use adoptive immunotherapy using Epstein-Barr virus (EBV) specific T cells to treat refractory or recurrent EBV expressing B cell lymphoma in human immunodeficiency virus infected patients. This type of clinical research holds great promise but requires specially adapted laboratories built to meet FDA requirements for Good Manufacturing Practices which include stringent quality controls. Those facilities will be introduced into several GCRC sites in FY 1996 to greatly facilitate investigators supported by the several NIH categorical institutes.

Biotechnology

Understanding protein folding and the ability to predict the tertiary structure of a protein from the amino acid sequence is one of the most important problems in theoretical molecular biology. While a complete solution to the problem is still not feasible, considerable progress has been made using high performance computing. A new algorithm has been developed that uses the NMR measurements of secondary structure to calculate the tertiary structure, i.e., the stable final form of the protein. Excellent results have been obtained on several proteins of known structure and future experiments on proteins of unknown tertiary structure are planned.

A new center was recently established to advance technologies related to neural communication, and to enable scientists to observe, understand, and influence the activities of nerve cells. One objective is to develop promising new microprobe technologies that will enable researchers not only to record nervous system impulses, but to deliver drugs, cellular growth factors, neurotransmitters, and other neuroactive compounds to single neurons or groups of neurons. Neural probes are now so small that they could one day be implanted in the brain and replace damaged or missing nerves.

In the U.S., there has been a progressive increase in the use of synchrotron radiation facilities, which provide high-energy x-rays essential for research by biomedical investigators. These facilities allow scientists to determine the three-dimensional structures of proteins, nucleic acids, and viruses by X-ray crystallographic methods. NCRR currently funds three synchrotron resources, and is funding construction of beamline development at the Argonne National Laboratory in Illinois to help address the progressively increased use of this sophisticated technology by biomedical investigators. By extending structural biology capabilities to include time-resolved studies of biochemical events that take place in fractions of a second in crystals, one of the new beamlines will give investigators unique research capabilities not available at other U.S. synchrotron sites.

The development of sophisticated molecular technologies can easily be adapted to marine organisms. Research into the basic developmental, cellular, and molecular aspects of these research models provide valuable information on processes that are common to organisms, from yeast to humans. Inch-long sea squirts that grow on boat bottoms, for example, have kidney-like renal sacs that contain a mineral also found in human kidney stones. Investigators are working to isolate and identify a substance in the sea squirt's renal sac that appears to inhibit crystallization 20 times more powerfully than anything in the human urinary tract.

Improved instruments and faster, more powerful computers are allowing scientists to view biological systems--from molecules to entire organ systems--using new noninvasive magnetic resonance imaging techniques that help uncover information on cell movement, cellular distribution, and cell kinetics in vivo. Ultimately the technique may prove clinically useful to detect organ rejection at an early stage following transplantation.

Legions of aquatic animals have been enlisted in the war against human disease. For example, studies of the abalone, a marine mollusc, have revealed that the death of unneeded cells is regulated by an orderly process called apoptosis or programmed cell death. Investigators have identified the first specific enzyme responsible for programmed cell death. Thus, abalone larvae may provide a useful new model for studies of development, aging, and diseases such as cancer, muscular dystrophy, and Alzheimer's.

As science enters the 21st century, NCRR is developing and making available to more scientists new biotechnologies such as induced mutant animals--transgenics and knock-outs. In FY 1993, NCRR established a National Resource for Induced Mutants. This center validates, preserves and distributes many newly developed strains that have significant scientific value to biomedical research. That cost-effective approach provides these important research animals to more investigators who do not need to develop the induced mutant de novo. In FY 1996, NCRR will expand its resources for transgenic and other targeted mutant animals because of the large scientific demand for this resource. With such precise models, it will be possible to study specific genes responsible for normal cell functions as well as for human diseases.

In FY 1996, NCRR will expand research and development of devices, instruments and methods for the prevention and control of disease and disabling conditions, and the reduction of health care costs. This program, initiated in FY 1995, will spur novel, cost-effective bioengineering approaches to develop microsensors, physiological monitoring systems, and "smart" drug delivery systems that could improve the quality and reduce the cost of health care.

NCRR also plans to encourage development of innovative software, algorithms, and techniques for "smart" network connected technologies. These and other technologies will facilitate biomedical, behavioral, and clinical research in computational biology, protein folding, sequence analysis, modeling/simulation (including molecular modeling), visualization/virtual reality, structure-based drug design, cognition/brain research, and large database access and manipulation.

Comparative Medicine

A steady and diverse supply of animal models is indispensable for successful biomedical research. To offer researchers a combination of model systems from which to choose, NCRR encourages their development, from "high connectivity" models--such as hydras, lobster hearts, and clams about which a large body of knowledge already is available and applicable to other systems--to AIDS animal models. For example, these efforts have led to the development of animal models to study respiratory distress in neonates. Treatment of monkey fetuses in utero with epidermal growth factor (EGF) stimulates functional and structural maturation of the lung. This markedly reduces the clinical severity in these models of respiratory distress syndrome (RDS), a major cause of human neonatal mortality. The study further suggests that both lower mortality and a lower incidence of bronchopulmonary dysplasia, a major complication of RDS, may result from EGF treatment.

As the U.S. population ages, certain diseases, including Alzheimer's and certain complications of menopause, will assume greater importance. Solutions to these health challenges will require animal models of various conditions and ages, making the development of these models a high priority. Likewise, expanding developments in reproductive biotechnology enable studies of normal reproductive processes and the production of normal, healthy, disease-free offspring. Isolation of embryonic stem cells from species other than mice will extend gene knock-out technologies to other species that serve as unique models for human disease.

Clinical Research Training

A recently published Institute of Medicine Report, Careers in Clinical Research. Obstacles and Opportunities, addressed a concern about the numbers of individuals pursuing careers in patient-oriented research. In response to that Report as well as the steadily decreasing number of physician investigators submitting new NIH grant applications, the GCRC program will continue to expand its successful Clinical Associate Physician program to try to increase the pool of successful patient-oriented investigators required to translate the advances in the laboratory back to the patient. This is especially important in this era when unprecedented opportunities exist not only to understand the basic mechanisms of disease but also to develop and use novel therapies for those diseases. Only licensed physicians can fulfill that role.

In addition, the GCRC program will initiate a Clinical Scholars program for physicians to devote one year of intensive study to a core curriculum which will include bioethics, experimental study and clinical trials design, Federal regulations for patient-oriented research, biostatistics, outcomes research, and other appropriate courses to meet a student's future career research goals. This program will serve as a bridge to junior career development to assure that young physicians will be trained in the basics of clinical research and will be positioned to receive mentoring through their junior career development. In a separate but related effort, formalized courses for patient-oriented research and hands-on training for selected novel technologies for patient-oriented research will be offered at GCRC sites to individuals in training as well as to established clinical investigators.

Infrastructure Improvement

One of NCRR's foremost objectives is to expand the U.S. capability for research in the health sciences by supporting predominantly minority institutions that offer doctoral degrees in the health sciences. Recipient institutions use funds provided through NCRR's Research Centers in Minority Institutions program to hire additional research faculty in the biomedical and behavioral sciences, support training in specialized analytical methods, upgrade facilities, purchase advanced scientific instrumentation, and conduct pilot projects. To date, nineteen institutions have received awards designed to increase the participation of minority institutions in biomedical research.

Institutional Development

In response to a Congressional initiative, the Institutional Development Award (IDeA) Program was first implemented in FY 1993. This program provides infrastructure support to institutions in states with historically lower levels of NIH competitive research funding. The primary goal of this peer-reviewed program is to enhance the competitiveness of research institutions in eligible states and thus broaden the geographical distribution of NIH funding for biomedical research. In FY 1993, six one-year awards were made for a total of $750,000. Seven two-year awards were made in response to a solicitation in FY 1994 and will extend through FY 1995. Approximately 10 new competitive awards will be made in FY 1996.

Research Facilities

In FY 1994, for the first time in 5 years, NCRR awarded competitive grants of up to $2 million to eight institutions to revamp their biomedical research facilities. Through its Research Facilities Improvement Program (RFIP), NCRR will continue to provide funds on an NIH-wide basis to address the need for replacement, modernization, and construction of basic and clinical biomedical and behavioral research facilities. NCRR launched this initiative in 1994 in response to Congressional recognition that a growing deficit in satisfactory research space significantly threatened progress in biomedical research. Congress also addressed the need to replace outmoded facilities, relieve overcrowding, and to accommodate changing research requirements, especially in institutions of emerging excellence, regional primate research centers, and institutions undergoing changing research requirements.

Several Research Facilities Improvement awards will help strengthen gene therapy research. One will help expand a center where an interdisciplinary research program employs emerging and novel technologies to directly benefit cancer and AIDS research, pediatric heritable diseases, and the human genome project. Another award will provide facilities for all services needed for the care and use of sheep involved in extensive fetal metabolism and gene therapy research. The third will provide research laboratories, core support facilities, and office space to establish a multidisciplinary genomic research center. Two additional competitive awards were made to historically black colleges, one to help repair a building that houses research including projects in tropical medicine, molecular biology, neurobiology, and infectious disease, and another award to an institution to help establish a Clinical Research Unit and an analytical laboratory to support research.In FY 1995 and FY 1996 approximately ten to twelve new awards will be made to enhance facilities in high priority research areas.

Minority Research Infrastructure

Scientists have long known that certain eye tissues can be reprogrammed and irreversibly transformed into other types of cells. Now investigators at Morehouse Medical College, supported by Research Centers in Minority Institutions (RCMI) funding, have issued the first report of epithelial cells from the adult human retina having been transformed into nerve cells. The new cell line, which was established using the simian virus (SV40) T antigen gene, will be invaluable to researchers who need cell lines of ocular tissues to investigate the origins of eye disease. Researchers at another RCMI-supported institution are developing a rodent model for Parkinson's disease that may help explain both the disease mechanism and the reason the most used treatment for Parkinson's disease--L-dopa--often loses its effectiveness.

Another RCMI-supported project sheds new light on nerve growth and regeneration. Recovery from nerve injury requires neuronal growth, but the myelin sheath, which surrounds nerves, appears to inhibit nerve recuperation in the central nervous system. Scientists at Hunter College have found that myelin-associated glycoprotein inhibits neurite outgrowth in cells of both the central and peripheral nervous systems in rats. This inhibitory activity suggests that the molecule may be responsible for the inability of nerves to regenerate in the CNS of whole animals. Research will continue in FY 1996.

In FY 1994, a partnership was formed to foster collaborations among eight RCMI institutions with affiliated medical schools and researchers conducting studies in NCRR-supported General Clinical Research Centers. Long-range, this Clinical Research Infrastructure Initiative will facilitate research on major health problems facing minority populations, such as AIDS and heart disease, and will help investigators at minority institutions hone their clinical research skills. The Initiative will provide competitive support for (a) faculty expansion and development, (b) specialized facilities and core laboratories needed for clinical research, (c) epidemiological studies, and (d) pilot projects. NCRR anticipates awarding two to four competitive supplemental awards in both FY 1995 and FY 1996, to enhance this initiative.

Human Resources Development

The Minority High School Student Research Apprenticeship (MHSSRA) Program continues as NIH's flagship program for attracting high school students to careers in biomedical research and the health professions. The program provides support for students who spend six to eight weeks during the summer gaining hands-on research experience in biomedical research laboratories. For the past three years, the program has expanded to include summer training experiences that allow K-12 teachers and pre-service teachers to update their knowledge of health-related science.

Two 17-year old students who participated in NCRR's Minority High School Student Research Apprentice (MHSSRA) Program were among the 40 finalists in the 1994 Westinghouse Science Talent Search, the nation's oldest high school science competition. This program will continue to produce outstanding young scientists in FY 1996.

The main goal of the Science Education Partnership Award (SEPA) program is to spur university-based scientists to work with educators and other organizations to improve student and public understanding of health-related science. The program initially developed a broad range of model programs. These included a national video education program, a traveling AIDS exhibit, biotechnology research experiences for students and teachers, and health promotion outreach for inner city and rural communities. The program has now moved to support finalization of model pilot programs as well as to support dissemination of well-tested programs for larger audiences in order to have a greater impact on students' understanding of science and the public's science literacy in the biomedical and behavioral sciences. New long distance learning methods should lead to dissemination of science education programs on a regional or national scale as well.

The Brain Link Project, developed through the SEPA program, helps middle school students, teachers, and parents understand basic and applied neuroscience research, healthy behaviors, and ways to prevent certain nervous-system diseases. Extraordinary efforts went into making classrooms materials an entertaining and interesting way to learn science and to promote science- and neuroscience-related careers. Four units--The Physical Brain, Motor Highways, Sensory Signals, and Memory and Learning--have been reviewed by scientists, edited by teachers, and tested by students, and have been exceptionally well received by all three groups. The units will be disseminated through a national network of users, and selected materials are being translated into Spanish. The Brain Link Project promises to have a significant impact on health/science education.

National Center for Research Resources

Research Management and Support

Authorizing Legislation - Sections 301, 479, 480, and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual		FY 1995 Current Estimate		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
98	$12,468,000	100	$14,114,000	98	$14,304,000	-2	+$190,000

The Research Management and Support activity provides the resources and staff necessary for the program management and scientific direction of the Center and its extramural programs. Scientific and administrative staff work together to plan, develop and carry out these programs in order to provide the extramural research community with the resources essential for the conduct of biomedical research. Administrative and managerial services are provided through the Office of the Director, the Office of Science and Health Reports, the Office of Science Policy, the Office of Grants and Contracts Management, and the Office of Administrative Management--including financial management, human resources management, and information resources management, as well as provision of general administrative services--to all components of the NCRR. The extramural review staff provides policy direction and coordination for all phases of scientific and technical review activities within the NCRR involving research grants, research training grants, and research and development contracts. The extramural program staff provides the planning, development, administration and monitoring of the extramural research programs of the NCRR, and serves in a liaison capacity for applicants, grantees, other components of the NIH, the Department and other science agencies, advisory bodies, and other interested groups in areas related to research resources.

Funding for the Research Management and Support activity during the past five years has been as follows:

	Amount	FTEs
FY 1991	$12,473,000	103
FY 1992	12,796,000	109
FY 1993	12,923,000	108
FY 1994	12,468,000	98
FY 1995	14,114,000	100

Rational for the Budget Request

The FY 1996 budget request for Research Management and Support is $14,304,000. This represents an increase of 1.3 percent over the FY 1995 estimate of $14,114,000. These funds will provide for built-in increases in personnel and other costs, as well as a portion of the costs of relocation of the NCRR Office of the Director.

National Center for Research Resources

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director.....	9	10	10
Office of Administrative Management..............	17	16	15
Office of Grants and Contracts Management.....	13	15	15
Office of Review...........	14	14	14
Office of Science and Health Reports...........	3	3	3
Office of Science Policy...	9	8	7
Biological Models & Materials Research.......	3	3	3
Biomedical Research Support.................	4	4	4
Biomedical Research Technology..............	5	6	6
Comparative Medicine.......	7	6	6
General Clinical Research Centers.................	9	9	9
Research Centers in Minority Institutions....	4	4	4
Research Facilities Improvement.............	1	2	2
Biomedical Engineering & Instrumentation..........	0	0	0
Library...................	0	0	0
Medical Arts & Photography..............	0	0	0
Veterinary Resources.......	0	0	0
Total, NCRR 1/.............	98	100	98

Average GS/GM Grade

1991...	9.9
1992...	9.9
1993...	9.8
1994...	9.8
1995...	9.8
1996...	9.8

Program Administration
Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Request
Executive level I	0	0	0
Executive level II	0	0	0
Executive level III	0	0	0
Executive level IV	0	0	0
Executive level V	0	0	0
Subtotal	0	0	0
Total - Exec. Lev. Sal.	0	0	0
ES-6	0	0	0
ES-5	1	1	1
ES-4	1	1	1
ES-3	0	0	0
ES-2	0	1	1
ES-1	1	1	1
Subtotal	3	4	4
Total - ES Salary			
GS/GM-15	8	9	8
GS/GM-14	15	14	14
GS/GM-13	9	7	7
GS-12	11	12	12
GS-11	3	4	4
GS-10	0	0	0
GS-9	5	4	4
GS-8	5	4	4
GS-7	14	16	16
GS-6	8	9	9
GS-5	7	8	8
GS-4	1	1	1
GS-3	1	1	1
GS-2	1	0	0
GS-1	0	0	0
Subtotal	88	89	88

Grades established by Act of July 1, 1994 (42 U.S.C. 207):

Assistant Surgeon General	0	0	0
Director Grade	3	2	2
Senior Grade	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	3	2	2
Ungraded			
Total permanent positions	94	95	94
Total positions, end of year...	95	100	98
Total full-time equivalent employment, end of year........	98	100	98
Average ES level...............	3.3	3.0	3.0
Average ES salary..............	$104,000	$103,000	$103,000
Average GS/GM grade............	10.1	10.0	10.0
Average GS/GM salary...........	$40,529	$41,826	$42,746

THURSDAY, MARCH 30, 1995.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. DUANE ALEXANDER, DIRECTOR
DR. YVONNE T. MADDOX, DEPUTY DIRECTOR
BENJAMIN E. FULTON, DEPUTY EXECUTIVE OFFICER
DONNA CASADY, ACTING BUDGET OFFICER
DR. HAROLD E. VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET DHHS

Mr. BONILLA [presiding]. The committee will now be in order.

This afternoon we're delighted to hear from Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development. Welcome, and if you'd like to introduce your colleagues that you brought along today, and proceed.

INTRODUCTION OF WITNESSES

Dr. ALEXANDER. I would, thank you, Mr. Bonilla.

On my right is Dr. Yvonne Maddox, our Deputy Director. On my left is Donna Casady, our Acting Budget Officer, and Mr. Ben Fulton, our Deputy Executive Officer.

OPENING STATEMENT

Mr. Bonilla, the exciting research mission of the National Institute of Child Health and Human Development encompasses an exceptionally broad spectrum of scientific challenges. The common thread that connects this spectrum is the emphasis on prevention of illness and disability, with the goal of improving the quality of life throughout the life span. Since many diseases and disabilities that occur later in life have their origins early in life, the NICHD is especially able to contribute to the health and well-being of all Americans.

Some 4,000 children are born each year with neural tube defects, or NTDs, such as spina bifida, which often result in costly life-long disabilities. An NICHD led research team has identified a metabolic defect that may be responsible for a large number of these NTDs, explaining the recent discovery that women who take folic acid early during their pregnancy or prior to it can dramatically reduce the risk of having a child with an NTD. This study suggests that the metabolic defect may be correctable with vitamin B–12 as well as folic acid.

Immunization has long been one of the pillars of preventive medicine, and the NICHD has had some notable recent accomplishments in this area. The adverse side effects associated with the pertussis vaccine that currently must be used for children less than 18 months old have caused a lot of concern.

Our Institute recently completed a clinical trial evaluating a new vaccine for pertussis. This vaccine, developed in our intramural laboratories, was found to be remarkably free of side effects and remarkably effective. The company that manufactures the vaccine under license from the NICHD will be applying to the FDA for marketing approval with the intent of introducing this safe vaccine to the U.S. as soon as possible.

I might add parenthetically that part of the clinical trials for developing that vaccine were conducted in San Antonio.

The benefits of an NICHD-developed vaccine licensed several years ago to prevent Hemophilus influenza Type b disease are now being seen. Some 15,000 cases of bacterial meningitis, a frequent complication of HIB, used to be reported each year, leaving thousands of children with mental retardation, deafness or learning disability. Now that the HIB vaccine is part of the routine recommended childhood immunization series, the incidence of this devastating disease has declined dramatically, with the expectation that the disease will be nearly eliminated in the U.S. within the next few years.

In another prevention effort, this past June NICHD initiated a nationwide campaign to persuade parents and other caregivers to place healthy babies on their back or side to sleep, to help reduce the risk of SIDS, the leading cause of death between one and twelve months of age. Preliminary reports from around the country indicate that the Back to Sleep campaign, some of the materials of which are displayed on the side table there, is succeeding in changing infant sleep position practice, although it's still too soon to indicate whether SIDS rates are changing as well.

In other prevention research focused on infant health and wellbeing, the NICHD's newborn intensive care network recently demonstrated that corticosteroids administered to mothers in danger of going into premature labor resulted in a 50 to 60 percent reduction in their baby's risk of death or suffering complications such as brain hemorrhage, respiratory distress syndrome, or chronic lung disease.

It's estimated that several thousand additional very low birthweight infants, many of them from minority groups, would survive each year if 60 percent of the mothers of the pre-term infants received prenatal steroids. Such use would result in a savings of more than $150 million per year in cost of hospitalization alone.

Currently, more than 20 percent of mothers delivering prematurely receive antenatal steroids. So the NICHD, based on these findings, is joining with the American College of Obstetricians and Gynecologists to actively promote the use of corticosteroids, so that more infants may benefit from this preventive therapy.

Prevention is also the focus of our research on AIDS. Our joint trial with the NIAID demonstrated that AZT is highly effective in preventing the transmission of HIV from a pregnant woman to her baby. We're now working with other public health service agencies to promote the use of AZT in HIV-positive pregnant women and conducting a trial to determine if adding hyperimmune globulin to AZT will further reduce transmission.

As another part of our AIDS research program, we've been working for several years to develop and test female controlled barrier contraceptives, as well as spermicides that would protect against pregnancy and sexually transmitted diseases, including HIV infection. Better chemical barriers, including spermicides and microbicides, are urgently needed, and NICHD supported researchers are working diligently to formulate new products.

Several studies have shown a notable decrease in cardiovascular disease among women who take menopausal hormone replacement therapy. The Post-menopausal Estrogen and Progestin Intervention trial, or PEPI, which the NICHD helped to support, provides the first data to indicate that hormone therapy improves a woman's risk factor profile for cardiovascular disease. Although definitive evidence for protection against cardiovascular diseases awaits completion of a large clinical trial, these results provide useful information for women and their physicians making decisions about hormone replacement therapy.

Even these few highlights provide ample evidence that prevention of disease and disability throughout the life span is the major priority of this Institute. Not only does this emphasis promote health and well-being, but the actual and potential savings realized by this research, prevention of neural tube defects, whooping cough, complications of preterm delivery, unwanted or unintended pregnancy, HIV infection, meningitis and cardiovascular disease, to name just a few, offset this Institute's annual budget many times over.

Mr. Chairman, the National Institute of Child Health and Human Development requests $526,177,000 for fiscal year 1996. I would be glad to answer any questions.

[The prepared statement and biography of Dr. Duane Alexander follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Child Health and Human Development

The exciting research mission of the National Institute of Child Health and Human Development (NICHD) encompasses an exceptionally broad spectrum of scientific challenges, ranging from expanding our knowledge of the basic biology of human growth and development, to identifying the factors that affect human behavior, to medical rehabilitation.

The common thread that connects this spectrum is the emphasis on prevention of illness and disability, with the goal of improving quality of life throughout the lifespan. Since many diseases and disabilities that occur in later years have their origins early in life, the NICHD is especially able to contribute to the health and well-being of all Americans. The NICHD research program helps to reduce the economic and human costs associated with disease and disability.

Some children, about 1 per 1,000 pregnancies, are born with neural tube defects (NTDs) such as spina bifida. These defects are fatal or leave the survivors with paralysis, mental retardation or other costly life-long disabilities. A research team led by an NICHD investigator has identified a metabolic defect that may be responsible for a large number of NTDs. This finding would explain the recent discovery that women who take folic acid prior to pregnancy or very early in pregnancy can dramatically reduce their risk of having a child with an NTD. Their study also suggests that the metabolic defect may be correctable with vitamin B12 as well as folic acid. This possibility has important public health implications. The U.S. and other countries have been considering fortifying food with folic acid to ensure that women at risk receive adequate amounts to prevent NTDs. If adding vitamin B12 to food could decrease the amount of folic acid needed, it might eliminate the concern about exposing some individuals to higher than recommended levels of folic acid and still prevent NTDs.

Immunization has long been one of the pillars of preventive medicine. All U.S. children are required to be immunized against diphtheria, tetanus, and pertussis (whooping cough). The frequency of adverse side effects with the pertussis vaccine currently used for children less than 18 months old has caused concern and prompted the search for a safer vaccine. The NICHD recently completed a clinical trial evaluating the effectiveness and safety of a new vaccine for pertussis. This vaccine, developed in the NICHD intramural laboratories, differs from currently used vaccines in that it consists of a single component, pertussis toxoid, rather than being composed of multiple parts or the entire bacterium that causes the disease. The NICHD vaccine was found to be remarkably free of side effects and to be very effective. Even though the clinical trial was conducted during a severe pertussis epidemic, only 4 percent of the children who received the vaccine developed pertussis while in the unvaccinated group, 14 percent of the children got the disease, giving the vaccine an efficacy rate of 71 percent. The company that manufactures the vaccine under license from the NICHD will apply to the FDA for marketing approval, with the intent of introducing this safer vaccine to the U.S. as soon as possible.

Another NICHD-developed vaccine, one to prevent typhoid fever, was recently approved for marketing by the FDA. While other typhoid vaccines are available, they require either multiple oral doses or injections, frequently cause side effects, and are not very effective. The new NICHD vaccine requires only one injection, is effective, and like the new pertussis vaccine, is virtually free of side effects. This vaccine has the potential to virtually eliminate typhoid as a major cause of serious illness in areas of the world where food and water sources are frequently contaminated with human wastes. It will protect U.S. travelers and military persons in those areas and eliminate the risk of typhoid in the U.S. and other developed countries when natural disasters such as floods or earthquakes damage sewage disposal systems.

The benefits of an NICHD-developed vaccine licensed several years ago to prevent _Hemophilus influenzae_ type b (Hib) are now being seen. Some 15,000 cases of bacterial meningitis, a frequent complication of Hib, used to be reported each year, leaving thousands of children with mental retardation, deafness or learning disabilities. Now that the Hib vaccine is part of the recommended routine childhood immunization series, the incidence of this devastating disease has declined dramatically, with the expectation that the disease will be nearly eliminated in the U.S. within the next few years.

Between the first and twelfth months of life, Sudden Infant Death Syndrome is the single leading cause of death. Some 6,000 U.S. babies die each year from SIDS. Last June, the NICHD initiated a nationwide campaign to persuade parents and other caregivers of newborns to place healthy babies on their back or side to sleep to help reduce the risk of SIDS. This recommendation is based on the observation that in other countries, the rate of SIDS has dropped 50 percent or more following changes in sleep position after similar public education campaigns. The NICHD has developed, in conjunction with the American Academy of Pediatrics and other sponsors of the campaign, brochures for both parents and health care providers, posters, public service announcements, a 1-800 information telephone line, videos and other materials to promote the Back to Sleep campaign nationally. Preliminary reports from around the country, including Maryland, seem to indicate that SIDS rates may have dropped within the past year. It is too early to say for sure that SIDS rates have dropped or that the campaign is responsible for any decline, but these early reports are encouraging. The NICHD is conducting a comprehensive evaluation of the campaign to assess its impact on parents, caregivers, providers and SIDS rates.

In other research focused on infant health and well-being, the NICHD Newborn Intensive Care Network recently demonstrated that corticosteroids administered to mothers in danger of going into premature labor resulted in a 50 to 60 percent reduction in their baby's risk of death or suffering complications such as brain hemorrhage, respiratory distress syndrome, and chronic lung disease. It is estimated that several thousand additional very low birth weight infants would survive each year if 60 percent of the mothers of preterm infants received antenatal steroids. Such use would result in a minimum savings of more than $150 million per year in the cost of hospitalization alone. Currently, it is estimated that fewer than 20 percent of mothers delivering prematurely receive antenatal steroids. The NICHD, based on the above findings, is joining with the American College of Obstetricians and Gynecologists to actively promote the use of corticosteroids so that more infants may benefit from this preventive therapy.

The NICHD also has a significant research interest in youth and adolescents. For African Americans between the ages of 15 and 24, violence is the leading cause of death. Research supported by NICHD provides the basis for developing and evaluating intervention programs to reduce violence and related behaviors in youth. With funding from the NIH Office of Research on Minority Health, NICHD supports seven projects to develop, implement, and evaluate coordinated programs of community based health behavior interventions designed to focus on strategies for decreasing violence-related injuries and death, sexually transmitted diseases, and unwanted or unintended pregnancies in minority youth ages 10-18.

Children usually recover better from an injury to the brain than does an adult. This is because the central nervous system of young children is marked by plasticity, the ability to compensate for the injury by making critical changes in the functional architecture of the brain. Scientists supported by the Institute's National Center for Medical Rehabilitation Research are using imaging technology to examine the functional reorganization of the brain in young adults who sustained brain damage at an early age. These studies will increase our understanding of the spatial, temporal, and functional limits of human brain plasticity, with the goal of enabling neurosurgeons to develop surgical interventions to maximize patients' functional capabilities.

The NICHD, as part of its AIDS research program, has been working for several years to develop and test female controlled barrier contraceptives, as well as spermicides that would protect against pregnancy and sexually transmitted diseases, including HIV infection. Better chemical barriers including spermicides and microbicides are urgently needed, and NICHD-supported researchers are working diligently to formulate new products. Preliminary results from clinical evaluations of new polyurethane condoms indicate that they have a very low breakage rate and that users prefer them over the latex condoms on the market today.

Last year we reported that the NICHD helped design and fund the large clinical trial in which zidovudine (AZT) therapy reduced by two-thirds the risk of transmission of virus from HIV-infected women to their babies. This summer a Federal report providing guidance and recommendations to assist health care providers make decisions regarding the use of AZT in pregnant women was released. NICHD staff chaired the U.S. Public Health Service Task Force that prepared this report and developed the treatment guidelines. This report will be instrumental in the rapid transmission of research findings to clinical application.

Several studies have shown a notable decrease in cardiovascular disease among women who take menopausal hormonal replacement therapy. The Postmenopausal Estrogen and Progestin Intervention Trial (PEPI), which the NICHD helped support, provides the first data to indicate that hormone therapy improves a woman's risk factor profile for cardiovascular disease. Although definitive evidence for protection against cardiovascular diseases awaits completion of a large clinical trial, these results provide useful information for women and their physicians making decisions about hormone replacement therapy.

Even these few highlights provide ample evidence that prevention of disease and disability throughout the lifespan is the major priority of the NICHD. Not only does this emphasis promote health and well-being, but the actual and potential savings realized by this research--prevention of neural tube defects, typhoid fever, whooping cough, complications of preterm delivery, unwanted or unintended pregnancy, HIV infection, meningitis, and cardiovascular disease, to name just a few--offset this Institute's annual budget many times over.

Mr. Chairman, the National Institute of Child Health and Human Development requests $526,177,000 for FY 1996. I would be glad to answer any questions.

CURRICULUM VITAE

NAME	Duane Frederick Alexander, M.D.
BIRTH	August 11, 1940, Baltimore, Maryland
MARITAL STATUS	Married Marianne Ellis, Washington D.C., June 23, 1963; two children
EDUCATION	Pennsylvania State University, University Park, Pennsylvania, B.S. Degree, Pre-Medical, 1962 Johns Hopkins University School of Medicine, Baltimore, Maryland, M.D. Degree, 1966
INTERNSHIP	Intern and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1966-1967
RESIDENCY	Assistant Resident and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1967-1968
MILITARY SERVICE	1968-1970: Surgeon (LCDR), U.S. Public Health Service, and Clinical Associate, Children's Diagnostic and Study Branch, National Institute of Child Health and Human Development, (NICHD) National Institutes of Health (NIH) Bethesda, Maryland 1971-Present: From Surgeon to Assistant Surgeon General, U.S. Public Health Service
FELLOWSHIP	Fellow in Pediatrics (Developmental Disabilities), John F. Kennedy Institute for Habilitation of the Mentally and Physically Handicapped Child, Johns Hopkins Hospital, 1970-71
LICENSURE	Maryland Board of Medical Examiners
CERTIFICATION	Diplomate, American Board of Pediatrics, 1973
POSITIONS HELD	
1971-74	Assistant to the Scientific Director, NICHD, NIH, Bethesda, Maryland
1974-78	Medical Officer (Staff), National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, DHEW
1978-82	Assistant to the Director, NICHD, NIH
1982-86	Deputy Director, NICHD, NIH
1986-present	Director, NICHD, NIH

HUMAN EMBRYO RESEARCH

Mr. PORTER [resuming]. Dr. Alexander, let me add my welcome to that of my colleague from Texas, and my apology for being a little late in being able to be here.

Let me begin by asking about human embryo research, a subject we discussed here last week with Dr. Varmus. If this type of research were approved, would most of it be supported by your Institute?

Dr. ALEXANDER. Initially, we expect that the majority of it would be supported by NICHD. But eventually, the ramifications and implications for this research affect a number of Institutes. Research in the National Cancer Institute, for example, research in the National Center for Human Genome Research and in other Institutes would certainly find applications from human embryo research.

Mr. PORTER. How many applications for human embryo research are pending which are consistent with the guidelines set down by Dr. Varmus' advisory group and the President?

Dr. ALEXANDER. We have presently in hand 71 applications for research involving the human embryo. Most of these would be consistent with the recommendations that were put forth by the panel.

Mr. PORTER. Can you describe for us the principal types of human embryo research that would be conducted, and the potential benefits of this research?

Dr. ALEXANDER. Most of the applications at the present time focus on issues related to in vitro fertilization and increasing its success rate. The research would look at the maturation of eggs, improvements in the techniques of culturing eggs and early embryos, as well as research around the ability of sperm to fertilize eggs in vitro.

We also have research proposals that look at ways to select the healthiest of embryos, ways to avoid selecting embryos with chromosome abnormalities or other developmental defects, and thus avoid implanting embryos likely to develop abnormally and select for implantation those that have the best chance of success of normal development.

We also have applications that look at other issues, for example, attempts to culture embryos in solutions that have a higher than normal glucose content that would look at questions related to the increased incidence of congenital anomalies in diabetic pregnancy, for example, and whether these happen at this earliest stage of development.

There are other studies that have the capability of looking at other issues related to birth defects. Our ability to understand the fertilization process has implications for both infertility treatment as well as the possibility of new approaches to contraceptive development. Research related to the oncogenes that are active in early embryonic development as a normal process that may become abnormal later and lead to the development of cancers also holds potential for knowledge gain and application.

Finally, one of the most exciting potential applications from this research relates to the potential uses of embryonic stem cells. These cells are what we call totipotent initially, they may develop into basically any kind of a cell. Then they begin to differentiate into certain types of cell lines, different kinds of tissues that they will become.

If we were able to obtain embryonic stem cells that have started to develop along a certain path, they have great potential for application in transplantation research, initially as bone marrow replacements. If we could develop ways to grow sufficient numbers of these cells they could serve as bone marrow replacement cells, without risk of rejection, because they would not be detected as foreign by the recipient.

Eventually it might also be possible to develop other cell lines of these early cells that could serve as tissue donors for nerve cells, for muscle cells, skin cells or other types of cells. So there's an enormous potential application there as well.

Mr. PORTER. I'm advised that Mr. Bonilla has a radio interview at 2:30, so Mr. Bonilla, I yield to you.

HISPANIC HEALTH

Mr. BONILLA. Mr. Chairman, thank you for doing that. I appreciate that very much.

Dr. Alexander, in your budget justification you state that your Institute will fund a group of studies that addresses many of the factors that affect child health among Hispanic subpopulations. Among the topics to be studied are infant mortality, chronic disease, migration, assimilation and intercultural differences. Could you elaborate a little more on where these studies will be conducted, and when they will be completed?

Dr. ALEXANDER. These studies were funded as a result of a request for applications on Hispanic health. Most of them focus on issues related to infant mortality, to migratory patterns, to assimilation issues, and will be conducted at different institutions around the country. I will have to supply for the record the specific institutions and the specific topics that those grants will be addressing, but that's the general gist of it.

Mr. BONILLA. I would appreciate that.

Dr. ALEXANDER. I'll be glad to do that.

[The information follows:]

STUDIES IN HISPANIC HEALTH

In August FY 1994, the NICHD awarded five new projects for the support of research on the social, demographic, behavioral, and cultural factors in Hispanic child health. the recipients of these awards, titles of their research proposals, and end dates for their projects follow.

Erickson, Pamela, I. University of Connecticut, Storrs, Connecticut. Socio-cultural context of Hispanic Adolescent Pregnancy. 7/31/99

Frisbie, W. Parker, University of Texas, Austin, Texas. Enigma of Mexican Origin Pregnancy Outcomes. 7/31/97

Gutmann, Myron P. University of Texas, Austin, Texas Intra-Ethnic Differences in Hispanic Child Mortality. 7/31/97

Kharrazi, Martin. California Public Health Foundation, Berkeley, California. Pregnancy Outcomes in Mexican and U.S. Born Hispanics. 7/31/95

Landale, Nancy S. Pennsylvania State University, University Park, Pennsylvania. Puerto Rican Maternal and Infant Health Project. 7/31/99

BREAST CANCER

Mr. BONILLA. Could you explain, Doctor, why your Institute has a role in breast cancer research?

Dr. ALEXANDER. We have specific interest in breast cancer in relation to the use of oral contraceptives and the use of post-menopausal hormone replacement therapy. Questions have been raised about the risk of breast cancer in relation to these two treatments, and they have not been resolved satisfactorily by studies that have been conducted to date.

We have recently funded a study that looks at breast cancer in relation to the pill and hormone replacement therapy. This study will be conducted at five sites around the country. They will be recruiting women from hospitals rather than tumor registries, so that we will detect these cases early. We will be administering questionnaires to women about their past exposure to oral contraceptives of various types, as well as to hormone replacement therapy, and also getting information from them on a number of other practices as well, questions related to smoking, exercise, questions related to reproductive history, questions related to a number of other areas as well.

The total amount of funding that we have related to breast cancer in fiscal year 1995 is about $4,300,000.

Mr. BONILLA. Because I noticed you requested an increase of almost a million dollars, and that's why I asked that. So it's primarily for the studies that you described?

Dr. ALEXANDER. It's primarily for the breast cancer and pill study, yes, it is. That study was funded last year, and it's just swinging into full scale operation and the increase will cover that increased activity.

AIDS

Mr. BONILLA. Doctor, could you tell the subcommittee what you think about yesterday's news reports that we all watched about the boy in Los Angeles who was infected with the AIDS virus at birth, but apparently fought off the infection and is now free of the virus at age five?

Dr. ALEXANDER. That's a very interesting case, and has created a lot of interest, not only scientifically, but obviously among the lay community as well. This is a child who very clearly was infected with the AIDS virus, acquired from his mother, either during pregnancy or during the delivery, and tested positive for that virus by culture at 19 days and again at 51 days.

But by a year of age, he had no sign of infection with the virus at all. We don't have an explanation for this. Various possibilities have been put forward, one of which is that the virus strain that he acquired may have been a defective one, so that it could not replicate effectively, or establish an ongoing infection. Another possibility is that somehow or other, he was able to, some aspect of his immune system allowed him to throw off this early infection and prevent the infection from becoming established. It's also possible that there may be some reservoir of infection in the body of this child that we have not been able to detect.

What it raises, though, is the first clear demonstration that infection can occur and be removed from the body by the body's natural defenses by some mechanism. And I think it points out the importance of this particular model of perinatally acquired infection as informative in terms of how the immune system might be stimulated or how the immune system might work in throwing off this virus.

It's also of interest that if you look at early pregnancy, abortus material, for example, either spontaneous or induced abortion, probably 50 percent of fetuses from infected mothers will show infection, based on the ability to recover the virus. But at birth, only about 25 percent are infected, again raising the question that something apparently is going on here at this time, and that the fetus, which has, as best we know, a much weaker immune system than the adult, is somehow able to throw off this infection.

So what it tells us is, there's something here that's going on of interest that we need to spend more time and effort and resources on studying.

Mr. BONILLA. Is the NIH already getting hold of those results and looking at that study?

Dr. ALEXANDER. Well, this study was funded by a combination of the NIAID and NICHD and the Fogarty Center. So we have been following this case along with the investigators, and are quite aware of it and its implications, and the need to follow through with the implications.

BIRTH DEFECTS

Mr. BONILLA. One final question, Doctor. Do you think that there could be any overlap between the newborn intensive care network and a birth defect surveillance program that would identify and address the causes of birth defects? I have a bill that I've introduced to set up regional clearinghouses to track birth defects, and I just want to make sure that they don't overlap in any way.

Dr. ALEXANDER. I don't think they do. Our neonatal intensive care network is really focusing on premature low birthweight infants and clinical trials involving these infants. The surveillance system that you propose to set up would have a quite different purpose, and I don't think they would overlap.

Mr. BONILLA. Thank you, Dr. Alexander.

And Chairman, again, thank you for allowing me to go out of turn.

Mr. PORTER. Thank you, Mr. Bonilla.

Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

Do I assume from Mr. Bonilla's comment that he was out of turn that it's your turn now?

Mr. PORTER. Could be. [Laughter.]

Ms. PELOSI. It will always be your turn, Mr. Chairman.

Mr. PORTER. Could be yours. [Laughter.]

Ms. PELOSI. But I know I should be grateful for going out of turn.

Mr. PORTER. No, no, no. Please just proceed.

FEMALE CONTROLLED BARRIER CONTRACEPTIVES

Ms. PELOSI. Thanks, Mr. Chairman. Thanks very much.

Dr. Alexander, welcome. Thank you for your testimony.

Let me commend you first of all for your efforts over the years to develop and test female controlled barrier contraceptives as well as spermicide that protect against pregnancy and sexually transmitted diseases, particularly HIV infection. Could you let us know the status of this research, and how long will it be before an HIV protective spermicide comes to market?

Dr. ALEXANDER. Well, there is an HIV protective spermicide on the market, nonoxynol 9, it's a component of most of the spermicidal jellies and very clearly has virucidal and bactericidal properties and the question is, is it as effective as it could be. The concern with this current product is that the vehicle in which it is contained tends to be irritating with very much use. And the concern is that the vaginal irritation could increase the risk for acquiring HIV, that would counteract the protective effect of the nonoxynol that it contains.

So a substantial portion of research is looking at nonoxynol and formulating it in different vehicles or in different carriers so that we might reduce the irritation component of this spermicide, and retain the virucidal and spermicidal properties of the nonoxynol.

We're also looking at other components that we might use as spermicides and microbicides. We have three contracts funded, looking at specific compounds. Two of those are now ready for clinical trials, and the third we expect to be ready shortly. The Population Council has also developed, in the center that we fund, a virucidal, spermicidal product that should be ready for testing very shortly.

There's also a new 24-hour effective nonoxynol compound that's under development and also about ready to test. In addition, we have contracts that are to be awarded during the current fiscal year for synthesis of additional products that would have both spermicidal and microbicidal properties.

So that work is underway, and I can't give you a specific date when new products will come to market. They range in their status from some just entering clinical trials to contracts about to be awarded to synthesize new products. But it's a very active area of research.

Ms. PELOSI. We have had on other occasions this conversation about the irritation caused by the spermicide that is on the market now.

Dr. ALEXANDER. Yes.

Ms. PELOSI. And what other risks that might pose. I wondered if you would describe what you just stated as promising, I know you can't give us a time table, but would that be described as promising?

Dr. ALEXANDER. Yes, I think it is promising. It's really, as I say, not the nonoxynol compound itself, but the carrier, the vehicle that it's compounded with to make it a jelly, to make it available. And we think we have a number of other possible vehicles or agents that it can be contained within to reduce the potential for irritation and make it a better product.

HIV TRANSMISSION FROM MOTHER TO CHILD

Ms. PELOSI. In early May our colleague, Congresswoman Morella, and I will be sponsoring a briefing for members of Congress on the CDC guidelines on prevention of HIV transmission from mother to child. To what extent has your agency been involved in developing these guidelines? Could you tell us why it is important to focus attention on outreach efforts to at-risk pregnant women?

Dr. ALEXANDER. Yes. The Institute has been involved in all stages in the development of these guidelines, beginning with the actual funding of the clinical trial along with the NIAID that demonstrated the reduction in transmission from mother to fetus by AZT treatment. Dr. Lynn Mofensen from our Institute chaired the Public Health Service Committee that was assigned to develop the guidelines to come from this particular trial. And she did so quite effectively.

We have met also with the American College of Obstetricians and Gynecologists to assist them in developing their own guidelines and make sure they're consistent with everyone else's. The PHS guidelines were published initially in August, in Morbidity and Mortality Weekly Report.

At the present time, AHCPR is engaged with us in developing a pamphlet for parents. This is a draft of that particular pamphlet, with information at a very easy reading level for pregnant women to help in their decision making as they are offered screening during pregnancy for detection of whether they are HIV positive or not. And the CDC's guidelines I think are to be published very soon. We also have been working very closely with them in that aspect.

So there's a whole bunch of different parts of this effort and NICHD has been involved with all of them.

NEWBORN SCREENING FOR HIV

Ms. PELOSI. I appreciate that. One of our colleagues, Mr. Ackerman, has legislation that would—and I hesitate to characterize ever since I heard Dr. Varmus' Nobel prize winning theory described last year when Dr. Fauci was asked a question, and he said, "I hesitate to answer, because I'm going to be describing Dr. Varmus' work to you in front of him in 30 seconds." But I hesitate to characterize Mr. Ackerman's legislation for fear of——

[Laughter.]

Ms. PELOSI. At the appropriate level, Pelosi to Ackerman, Fauci to Varmus. But in any event, the reason I raise that legislation is because in it, he talks about hospitals testing children for HIV and making their HIV status known to the mother. And it's very appealing. Yet the guidelines would say that we might lose some other opportunities in prevention and collecting epidemiological information if we go that route. Could you comment on that, please, Doctor?

Dr. ALEXANDER. Well, the best time for screening is during pregnancy, because then we have the opportunity for prevention. Screening a newborn gives you an opportunity to provide some treatment, but the opportunity for prevention has escaped. So I think that the major effort that we are making is toward voluntary screening, but very strongly encouraged voluntary screening of all pregnant women for HIV status. If that is implemented as effectively as it could and should be, then the issue of newborn screening with identifiers almost becomes a moot one, because we will have identified the at-risk population ahead of time. And at a time when the optimum opportunity for intervention, when prevention is possible, can be done.

We would hate to lose the opportunity that the anonymous newborn screening that's going on at the present time in 45 states provides. This is the best epidemiologic tool we have for following the course of this epidemic. And to no longer be able to do this anonymous screening on all newborns would be a significant loss to our public health efforts to track the spread of this epidemic. Again, if pregnancy screening has not occurred, what is recommended by the Public Health Service and by the Academy of Pediatrics is strongly encouraged newborn screening with identification, but on a voluntary basis, rather than a mandatory basis.

In places where this has been tried and implemented, the success rate of the voluntary newborn screening has been in excess of 95 percent. So we know it will work. We are concerned that mandatory screening with identifiers would have a detrimental effect, both on women's coming for prenatal care, women's allowing this to happen, and on our ability to do the newborn screening anonymously to track the spread of the epidemic.

Ms. PELOSI. Well, that helps a great deal in responding to my colleagues who are very eagerly signing on to the legislation, which I admit sounds appealing. But it certainly has some opportunity costs, as you have described, and I thank you very much for that. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Pelosi.

HUMAN EMBRYO RESEARCH

Dr. Alexander, a case at George Washington University recently made headlines in which researchers apparently cloned human embryos without the knowledge or approval of their supervisors. Does this action violate any current law or regulation? And would such research be permitted under the guidelines permitted by Dr. Varmus' advisory council?

Dr. ALEXANDER. There are two parts to the question. First, the procedural issue of whether the conduct of that research violated regulation. Since the research was not funded directly by the Department, the regulations technically do not apply to that, other than the part that says the Department will hold the institution and its IRB basically accountable for all research that is conducted at that institution, to assure that it complies to whatever standards the institution sets up. It should be compatible with the Department's expectation.

In this case, that research was conducted without IRB approval and thus violated the institution's guidelines for the conduct of the research. So in that respect, the procedural aspect was flawed.

The other part of your question relates to the science, and whether the scientific activity that was conducted would be permitted under the recommendations of the panel that reported to Dr. Varmus. As I recall the recommendations of that panel, cloning experiments of the type done were not to be permitted, and so that that research would not go forward. I believe that's correct.

CONTRACEPTIVE AND INFERTILITY RESEARCH CENTERS

Mr. PORTER. Could you bring us up to date on your contraceptive and infertility research centers; have the centers had the resources to conduct clinical trials or are they limited to the support of basic research? And is there a backlog of contraceptive clinical trials that are ready for startup?

Dr. ALEXANDER. The work in the contraceptive and infertility centers has proceeded primarily in terms of developing new products for testing and in basic work and in animal work. The contraceptive centers in particular have been proceeding with research related to development of contraceptive vaccines. The center in Connecticut has identified two specific proteins on the sperm that are potential antigens and has developed vaccines against these. And these are currently under test in monkeys. They're not ready for human tests yet.

The University of Virginia has identified another candidate protein antigen on sperm, and is proceeding with monkey trials as well. Those also are not yet ready for human studies.

We do not have at present the resources to do clinical trials in those centers with the amount of funding that is presently available, either in infertility or in the contraceptive arena.

SURVEY OF AMERICAN SEXUAL BEHAVIOR

Mr. PORTER. Thank you. Last fall, a survey of American sexual behavior was released with considerable media attention. The survey initially was going to be supported by your Institute, but after Congressional reluctance to fund the survey, it was financed by private foundations. In the debates about funding these sensitive surveys, it is sometimes argued that taxpayers' funds should not be used, that the private sector should take responsibility. Does last fall's survey confirm the point that the private sector has the resources to finance such surveys?

Dr. ALEXANDER. The private sector has the resources to fund them on a smaller scale. What happened was that this particular survey was scaled back massively from what had been originally planned, so that a much smaller sample was obtained. It was still a somewhat representative sample. But there is much less confidence about the validity of the data than might have been the case had the survey proceeded on the larger scale that was originally planned, with the resources that the Federal Government could have provided.

So I think the answer to your question is that in some instances, the private sector can come in and provide some resources to do studies on a scale that provides some answers, but not really to support studies of the magnitude that are most desirable to get answers to questions like these.

NICHD PERINATOLOGY RESEARCH BRANCH

Mr. PORTER. Your perinatology research branch at Georgetown University last year reported the world's first successful fetal surgery. What research areas is this branch targeting, and is it research that cannot easily be undertaken elsewhere?

Dr. ALEXANDER. The research that this branch is targeting relates primarily to issues of detection of congenital anomalies and successful interventions for them, the causes and treatments for premature labor, and other problems that increase infant mortality, particularly among minority populations. These studies are, in fact, being conducted in other places as well.

But the focus here is on really state-of-the-art diagnostic technology with ultrasound, and bringing together a corps of investigators that is difficult to assemble in any one site in the academic sector. These investigators, under the leadership of Dr. Roberto Romero, who's one of the most outstanding investigators in perinatal medicine, hope to be able to accomplish by the critical mass of scientific capability and resources that we hope to put together at this site, more than might be done in other locations to address the particular problems.

So I think that there is great value in an intramural laboratory and clinical program like this. There are studies like these on similar problems going on elsewhere. But I think we have the capabilities of doing them on a scale and with a quality that is unmatched.

Mr. PORTER. So this perinatology branch is fully established?

Dr. ALEXANDER. Not yet. It has been running somewhat behind because of delays in getting renovations done, so they actually started on site in July of last year. They plan to staff up steadily over the course of several years, and have not yet reached their full operating strength.

Mr. PORTER. Do you feel comfortable running this intramural program by contract?

Dr. ALEXANDER. We would rather be able to operate it directly. But in this case, we have directives from the Congress to operate it at a site in the District of Columbia. The best way to do it in this particular case is by contract for the provision of site, facilities, services and support. Our hope is eventually that most of the scientific personnel would be Government employees with the contract providing mainly the support personnel and services, the access to patients and the facilities to do the work.

DIAGNOSIS THROUGH COMPUTER ASSISTED IMAGING

Mr. PORTER. And my last question before I yield to Mrs. Lowey, can you tell us about recent advances that may permit diagnosis of disease in the human fetus through computer assisted imaging? Will this someday permit in utero treatment?

Dr. ALEXANDER. We believe that the whole purpose for all of our prenatal diagnostic activities is that it will lead eventually to treatment. The computer assisted diagnosis for the fetus is a relatively new venture, and I think that the capabilities of these techniques, as they are further explored and exploited, will allow us to detect anomalies earlier, at a time when they are potentially correctable by some of the manipulations that Dr. Romero has started to pioneer in the perinatology research branch.

The access to the fetus that we are getting with the capabilities of ultrasound, with fiber optics that allow us to really see inside the uterus directly and perform manipulations on the fetus, are really going to allow us to increasingly intervene for congenital anomalies, and in particular, to provide some corrections for things that otherwise would be fatal.

Mr. PORTER. Thank you, Dr. Alexander.

Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

BIONUTRITION AND PREGNANCY

Many of the questions have been asked, but to follow up, I've been interested in the issue of bionutrition. I know that the NICHD does support trials that explore the relationship between bionutrition and pregnancy. Could you update the subcommittee on your work in this area?

Dr. ALEXANDER. Yes. One of the studies that is in this area doesn't sound very fancy, because it's looking at calcium, the simple element calcium in nutrition, in pregnancy, and whether supplemental calcium given to women during pregnancy may in fact reduce their likelihood of developing preeclampsia, premature labor and premature delivery. We have a trial that's about three-fourths completed involving about 2,500 women that will I hope give us a definitive answer on this question.

Other studies relate to other simple dietary components or nutrients. A study was recently reported from one of our sister Institutes, the Neurology Institute, suggesting that magnesium given to women during delivery for treatment of preeclampsia when it had developed was associated with a lower incidence of cerebral palsy in their offspring. This raises very important questions about the role of magnesium as a way of reducing the incidence of cerebral palsy.

Other studies being conducted in our networks look at vitamin A, for example, as a way of preventing either chronic lung disease or brain hemorrhage in the newborn infant. These are studies that are under way at the present time in our maternal fetal medicine network.

TEENAGE PREGNANCY

Mrs. LOWEY. Thank you. I also understand that NICHD has supported research on demographic and behavioral sciences to provide information on factors affecting a range of issues including teen pregnancy. Do you have any data on that? What can you tell us, or what kind of information do you have that impacts the whole issue of teenage pregnancy?

Dr. ALEXANDER. The scientists at that particular branch have been at the forefront of gathering data and analyzing it relating to teen pregnancy. They just presented a paper last week that I would like to share with you that's an extensive analysis of the whole problem of teen pregnancy.

Basically, what we know is that sexual activity among teens has continued to increase, that by age 20, 80 percent of teenagers have had sexual intercourse, and many of them are regularly sexually active. We know that teenage pregnancy numbers had gone up, started to decline, and are now starting to go back up again. But the percentage of all births that are to teens has actually decreased.

We do know the adverse impact, socially and economically, of teen birth. This is a significant issue in the whole welfare system.

We do know some things that are likely to decrease teen pregnancy rates. We do know that access to family planning services significantly decreases pregnancy without increasing the incidence of sexual activity. We do know that teens can be effective contraceptors. Actually, teens are more effective at use of contraceptives than unmarried women in their 20s are. So we do know that when they are provided with access to contraceptives, they are pretty good users, but not as good as they should be.

We do know also that there are programs that are effective in postponing or discouraging sexual activity. These programs range in their types of approaches, but in general, they encourage teens of both sexes to delay their sexual activity, postponing sexual involvement is the catch phrase, until they are older, and succeed to varying extents in achieving that objective.

We don't have all the answers by any means on the whole problem of teen pregnancy. We have a number of studies underway that are looking at this question. We have some that have been reported showing varying success rates, but we don't have any final answers by any means on this whole problem of teen pregnancy.

SCHOOL-BASED INTERVENTION PROGRAMS

Mrs. LOWEY. We know that schools are often the place where we can intervene successfully or effectively for the simple reason, that's where you can actually have contact with the teens. Could you discuss with us any interventions that have been particularly successful in the schools? What are we learning about the role of schools?

Dr. ALEXANDER. There's been a lot of interest in school-based clinics as an approach to the teen pregnancy problem. Some address teen pregnancy primarily or alone. But the ones that seem to be most effective are much more broad in their approach and provide a whole range of health services to teens. These clinics have been evaluated and they vary in their effectiveness. But there is no question that this is—it can be an effective approach if done well, and that the incidence of teen pregnancy does go down when you have an effective school-based clinic program.

I think the studies that have been done here give us good indicators of what the characteristics are that make for an effective school-based clinic program and provide effective guidance for communities that are interested in establishing one.

Mrs. LOWEY. I think my time is finished. Thank you, Mr. Chairman.

Thank you.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Hoyer.

Mr. HOYER. Mr. Chairman, thank you. I don't have any questions, but I did want to come. I apologize, Doctor, for being late. I've been on the floor doing the scheduling with the majority leader. And as a result, I didn't get to hear you give the testimony, but I'm reading it now, and I want to thank you for all you're doing.

Dr. ALEXANDER. Thank you.

Mr. HOYER. And I will read the transcript of your testimony. Thank you.

CHILD CARE

Mr. PORTER. Thank you, Mr. Hoyer.

Many parents are concerned about the impact of child care on their children. The studies released to date seem contradictory, some indicating that child care threatens parent-child bonding and slows development, others suggesting that high-quality child care has positive effects. Your Institute is presently conducting a study of child care. Can you tell us anything at this stage about the results of that study and your assessment of the existing body of research?

Dr. ALEXANDER. Yes, Mr. Porter. This is a major undertaking for this Institute. Some years ago, we became concerned about the increasing dependence of parents on day care, and particularly a trend towards its increasing use in infancy. And therefore we established under cooperative agreements a ten-site network for a cooperative study of early child care. The study has enrolled nearly 1,100 infants and their families. They are followed now through age three, and we are just starting to get the data on the effects of day care on family relationships, on infant development, on intellectual function, on behaviors, and a number of other measures.

The initial results from this are going to be reported, I guess they're actually being reported as we speak, at the Society for Research on Child Development meeting in Indianapolis. The data are complete now for analysis only through age six months. What we have so far is indications of the measures of the quality of care and the basic demographics and the utilization of child care by the families in the study.

We have completed the evaluations of these children through age three. We are currently reviewing a proposal to extend this study through age seven, so that we'll be able to follow these children as they enter school and see what impacts, if any, there are, of this early day care experience on children by school age.

SMOKING AND INFERTILITY

Mr. PORTER. Your Institute has supported a research study which seems to indicate that in addition to its other harmful effects, smoking increases infertility. Is this association well established? Is it the same for males and females? Or is further research required?

Dr. ALEXANDER. The association is not a strong one, otherwise we'd have an awful lot of infertile people, more than we do. But the association is one that probably works by interfering with sperm function or with some ability of sperm to bind with the egg. We don't have enough information yet to really gauge this, and I really can't speak any further to it than that, because as you suggest, more research would be indicated to explore this as a possibility. It's, however, an easily correctable cause of infertility.

RESEARCH ON THE CAUSE OF SIDS

Mr. PORTER. Last year, your Institute spearheaded a campaign to make parents aware that sleep position has an impact on the risk of sudden infant death syndrome. Beyond this finding, which was based on an observational study, have you funded any recent research which may lead to answers about the cause of this bewildering syndrome?

Dr. ALEXANDER. The search for a cause for SIDS continues. The closest thing we have to a link that explains the association between sleep position and SIDS is anatomical findings from the studies of brain and brain stems from infants who have died of SIDS compared to normal infants that have died of other causes. And here we have found abnormalities in some of the nuclei of the brain stem that relate to the detection of oxygen and carbon dioxide levels in the blood, and the responses to these levels in terms of cardiac and respiratory function and sleep and wakefulness states.

Among the infants that have been studied, some of them have shown either absence of this nucleus or decreased numbers of neurons in this nucleus that would suggest a possible mechanism that would explain this correlation. And if in fact this is a mechanism, presumably how it would work would be that the infant placed on its stomach to sleep would turn its head into the covers or into the mattress or something else that's placed in the crib inappropriately, and as it breathes, it accumulates carbon dioxide, reduces its oxygen saturation but does not respond to this by turning its head to the side like a normal infant would. These infants, then, because of this brain anomaly, would be the ones who are more susceptible to SIDS and would represent the SIDS casualties.

SINGLE DOSE VACCINE FOR CHILDREN

Mr. PORTER. What is the state of research in identifying a single dose immunization vaccine for children? Is the U.S. the major supporter of this research, which has such important implications worldwide?

Dr. ALEXANDER. This is an effort by the World Health Organization, and the United States is a major participant in this. It's called the Children's Vaccine Initiative. At the present time, we do not have the technology for a single dose vaccine. However, developments such as the conjugate vaccine technology developed in Dr. Robbins' laboratory in our intramural program, and other approaches, looking at different types of adjuvants, suggest that we might be able to come close to this within some years. But it's going to take a lot of additional research.

We may never be able to get to the one-shot vaccine. The ideal really has been to not even have it have to be administered by injection, but an oral vaccine. And I think that is highly unlikely. But we are going to be getting much closer to it. At the present time, our ability to combine a number of antigens that would stimulate antibody production on a single carrier has increased. We are now giving as many as four or five vaccines in one shot at the present time. And we can probably get better than that.

CHILDREN'S DIET AND BEHAVIOR

Mr. PORTER. Your budget justification describes recent research supported by your Institute that indicates that the consumption of sugar has no impact on children's behavior, specifically on hyperactivity, which I'm sure will surprise some parents. Does this call into question the validity of various links that have been established between children's diet and their behavior?

Dr. ALEXANDER. I think it does. What this study did for the first time was really do a randomized, blinded control study of the sugar content in children's diets, and looking at very careful measures, objective measures, of their activity in a blinded fashion. And when the study was done that way, with all the biases and presumptions removed, there was no detectable difference in the children's behavior in relation to the sugar content of their diets.

Mr. PORTER. Mrs. Lowey? We're on round two now.

Mrs. LOWEY. I'll pass on this one.

Mr. PORTER. All right, Mr. Hoyer.

Mr. HOYER. I have no questions.

MEDICAL REHABILITATION RESEARCH

Mr. PORTER. The National Center for Medical Rehabilitation Research is faced with a broad array of research issues that must define its priorities rather narrowly given its resource level. How does the Center establish priorities for its research agenda? Parenthetically, I raise the question because your budget's description of the Center's research activities includes a study of access to nature trails for the disabled. I'm sure no one questions whether this is a worthwhile activity. But I'm a little surprised that it was judged a high enough priority to merit funding, given the current fiscal constraints.

Dr. ALEXANDER. Yes. Our priorities are established through a very active planning process. The legislation that established the Center directed that the first activity be the development of a research plan for this Center, with priorities. This was developed by the National Advisory Board that the Congress also directed be a component of the Center to advise and guide its activities. This board is two-thirds scientists and one-third lay in its representation. That plan was completed within 18 months with active involvement and primary responsibility by the national advisory board.

The priorities then have been set in conjunction with the recommendations included in that plan, and continued interaction with the advisory board and the council of the Institute. Research has proceeded, looking in large part at assistive devices and technologies that could help persons with disabilities, at neurologic rehabilitation efforts and activities, at problems with skin, decubitus ulcers, for example, and attempts to heal those, and various behavioral issues.

The particular grant that you mention is one that is quite different and quite unusual. But it relates to the whole concept of mainstreaming or integration of persons with disabilities into society. This was a Small Business Innovation Research grant, a $50,000 grant, to a company that is headed by a bioengineer who is disabled as a result of a neck injury, and in a wheelchair.

He is an avid outdoorsman and has been looking for ways to increase the accessibility of outdoor activities to persons with disabilities, and particularly persons in wheelchairs. He has engaged his company in various applications of technology, motorized wheelchairs, skis that will assist persons with disabilities, amputees or whatever, in skiing, and various other technological developments, to make it possible for persons with disabilities to participate in this aspect of normal life as well.

ACCESS FOR PERSONS WITH DISABILITIES

As a hiker before his injury, he was particularly interested in ways that people in wheelchairs might be able to have access to nature trails, if you will. And he put in this application for computer technology applications to evaluate the accessibility of nature trails to persons with disabilities in the national forests and the national parks.

What he did was develop ways of assessing things, not just simple things like the width of bridges in comparison to the width of wheelchairs, but how hard or how compact the surface of a trail was, to allow a chair to pass on it, or how rocky it was and how high the obstacles were for a chair. And then using sophisticated computer technology, he was able to develop computer profiles of trails that indicated all the obstacles that a person in a wheelchair might encounter. This then can be placed either at a visitor center or at the entrance to a nature trail so that a person coming to a park or a national forest with a disability would have that information available to them.

Now, this helps not just the people with disability, but ordinary hikers like you or me, who might not want to or be able to climb over huge obstacles or something particularly steep, and so all this information on trails and their nature and their accessibility and user-friendliness, if you will, is available and accessible to everyone. And I think it's created a lot of interest in the Park Service and the Forest Service for its adaptation and utilization in their trails, as part of their efforts to make their systems accessible to persons with disabilities.

Now, is this an appropriate NIH activity? You might raise the question that it's not necessarily biomedical research. But it's certainly an application of technology to enhancing the life opportunities and normalization, if you will, for persons with disabilities. So I think it's justifiable.

Mr. PORTER. Dr. Alexander, we have a number of additional questions that we would like to submit for the record.

We very much appreciate your good testimony and your forthright answers, and the job that you are doing there at the Institute. Thank you for coming here to testify.

Mr. Hoyer, yes.

STATUS OF THE HEALTH OF CHILDREN

Mr. HOYER. Doctor, if this has been answered, I've read your statement, forgive me. And I wonder how you assess, based upon the information you are exposed to, the health of children in America today as opposed to, say, 10 years ago?

Dr. ALEXANDER. I think overall the health of children is better. There are diseases that have been basically eliminated through vaccination, through other ways that we have developed through research. Our infant mortality rate, though still too high, has come down significantly and continues to drop. Our children, I think, overall, are healthier, and enter school healthier than they did probably ten years ago. So I think overall we have made significant improvements in children's health status.

There are still far too many children who are not participating fully in the benefits that we have to offer from our health care, whether it's through full immunization, through prenatal care that would have helped enhance their prenatal development, or through stimulation that's been provided to them, or through other health care measures and diseases that could have been prevented with earlier treatment or intervention.

SUBSTANCE ABUSE IN PREGNANCY

Mr. HOYER. Do we have a greater number of children, statistically, you may not know this, that are damaged by substance abuse of their mother, or just the use of substances, maybe not even the abuse, but the use of substances during the course of pregnancy, than we had before? Crack babies, obviously, are a particular example, HIV/AIDS, another one. But are there, in that context, increases in fetal alcohol syndrome?

Dr. ALEXANDER. Yes. Probably there's not much difference in fetal alcohol syndrome. Clearly the incidence of AIDS babies is up. We hope that if we are able to implement the AZT treatment regimen that has been developed that number can start to come down.

The incidence of crack babies, if you will, the mothers using cocaine and having an infant who has been exposed to it, is probably on the decline at the present time. What we still don't know is the long-term effects of that cocaine use. We have several studies ongoing at the present time following cohorts of infants whose mothers have used cocaine to various degrees and other substances as well during their pregnancy, to try to get an answer to what the longer-term impact of this is.

There was a lot of concern several years ago with people who believed there was actually a syndrome, the crack babies. That seems to have died out. We're no longer quite certain that there is such a specific syndrome. But there may well be longer-term or subtle problems that these infants have. The difficulty is teasing out the effect of the cocaine use during pregnancy from the effects of the environment in which they grow up.

Mr. HOYER. Thank you, Doctor.

Mr. PORTER. Thank you very much, Dr. Alexander.

[The following questions wre submitted to be answered for the record:]

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of centers supported in 1995.

Dr. Alexander: The information follows:

Number	Subject Matter
15	Mental Retardation
3	Learning Disabilities
9	Perinatal Research
19	Child Health Research
16	Reproductive Sciences
3	Contraceptive Research
2	Infertility Research
11	Demographic and Behavioral Sciences
78	Total

ADD HEALTH STUDY

Mr. Porter: Describe the design, annual and total cost, schedule and major subject areas of the adolescent health survey.

Dr. Alexander: The adolescent health study, or Add HEALTH as it is called, is a nationwide, comprehensive study of the complex forces that promote good health and well being for our young people, and those forces that put young lives at risk. It includes measures of general health status, medical conditions, height and weight, use of health services, injuries, physical disability, mental health, and sleep and eating disorders. It also focuses on health-related behaviors such as smoking, alcohol and drug use, violence, sexual behavior, contraception, exercise, nutrition, seat belt and helmet use, and others. The study features a longitudinal, multi-level design with independent measurement at the individual, family, peer group, school, and community levels.

The estimated cost of the study over a five-year period is $23 million, about $13 million of which has been incurred in FY's 1994 and 1995. Total costs for FY's 1996 through 1998 are estimated at $7.2 million, $1.6 million, and $1.0 million, respectively. Twelve component organizations in the U.S. Public Health Service are cooperating to fund the study.

FUNDING FOR RESEARCH AREAS

Mr. Porter: Identify 1994-1996 direct (not related) spending for the following: pediatric AIDS (with a separate breakout of funding for clinical trials), sudden infant death syndrome, mental retardation, Rett syndrome, contraception, infertility and fibroids/endometriosis/pelvic inflammatory disease.

Dr. Alexander: The support levels for these research areas are as follows.

(Dollars in thousands)

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
Pediatric AIDS........	$44,087	$45,900	$47,500
(clinical Trials)....	23,203	24,600	25,400
Sudden Infant Death Syndrome			
Total...............	41,569	42,800	44,000
Primary.............	10,766	11,100	11,500
Mental Retardation....	55,097	56,700	58,400
Rett Syndrome.........	1,647	1,800	1,854
Contraception.........	31,465	34,400	37,200
Infertility...........	10,825	11,100	11,400
Fibroids/endometriosis/ pelvic inflammatory disease............	2,278	2,400	2,500

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Porter: Provide a 1994-1996 mechanism table for the National Center for Medical Rehabilitation Research, including intramural research and RMS.

Dr. Alexander: The support levels for the National Center for Medical Rehabilitation Research by funding mechanism are as follows.

(Dollars in thousands)

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate
Research Project Grants..	$10,752	$11,656	$12,620
Research Centers.........	---	---	---
Other Research Grants....	377	390	400
Research Training........	2,066	2,430	2,430
R&D Contracts............	1,000	531	550
Total Extramural......	14,195	15,007	16,000
Intramural Research......	221	224	230
RMS......................	1,586	1,598	1,640
Total.................	16,002	16,829	17,870

SIDS

What is the five year spending plan associated with the second five years SIDS plan?

Dr. Alexander: FY 1995 is the first year of the second 5- year plan. NICHD is currently finalizing the second 5-year plan which will be submitted to the Appropriations Committee shortly. Since the development of the plan is still underway, there is currently no specific funding level associated with it. Preliminary estimates indicate, however, that approximately $15.3 million would be required to fully meet the plan's objectives in FY 1996.

BEHAVIORAL RESEARCH

Mr. Porter: Your Institute has one of the larger behavioral research portfolios at NIH. For the benefit of new Member's how do you respond to concerns that behavioral research is tangential to the basic biomedical mission of NIH?

Dr. Alexander: The NICHD defines its mandate broadly, to include research that examines the normal processes governing the growth and development upon which the health of children, youth, and families depends. These include biological, mental, behavioral, cognitive, socio-demographic and related processes that drive or influence the transformation of a single cell into a healthy, productive individual. Clearly, human behavior affects health outcomes. Thus, the NICHD supports projects designed to understand the linkages between behavior and health, and their implications for effective interventions.

Mr. Porter: To use one example that comes from your budget justification, why is it appropriate for your Institute to be researching preventing problem behavior among middle school students?

Dr. Alexander: This project on preventing problem behavior among middle school students involves a study to test the effectiveness of school-based interventions aimed at preventing risky behaviors (such as substance abuse, misconduct, violence and delinquency) that lead to adverse health effects. Several program components are being examined closely, including interventions that:

- improve students' social skills and conduct;
- enhance the school environment to increase student participation and sense of belonging; and
- involve parents in the promotion of positive behaviors.

A basic premise of this effort is that it is critical to help middle school children before they develop problem behaviors that are difficult to change in adolescence. Such prevention efforts may ultimately reduce the adverse health effects associated with risky behaviors, many of which are increasingly common among youth.

ADD HEALTH STUDY

Mr. Porter: You are conducting a survey of adolescent health that is mandated in your authorizing law. Can you describe for us the types of data that are being collected and how you have organized the data collection activities?

Dr. Alexander: The adolescent health study, called Add HEALTH, is a nationwide, comprehensive study of the complex forces that promote good health for our young people, and those forces that put young lives at risk. The study features a longitudinal, multi-level design with independent measurement at the individual, family, peer group, school, and community levels.

The data collection phase of the study started last fall with the administration of a short questionnaire to all seventh through twelfth graders -- over 100,000 students -- in a scientifically chosen sample of up to 160 middle and high schools nationwide. Parents were informed, before the questionnaire was administered in the schools, and had the opportunity to withdraw their student from the study. Administrators at each school were asked to provide information about the school's characteristics. Now, more extensive interviews are being conducted with 20,000 of the students in their homes. A parent of each adolescent in the study completes a questionnaire at the same time. Both the student and parent must give their written consent to participate. These interviews will include information about the adolescent's characteristics, health status and health behaviors, and the family environment. One year later, the young person will be interviewed again. Local indicators, such as housing, church attendance, unemployment rates, and health services will provide information about constraints and opportunities in the local community.

Young men and women will be represented equally in the sample. Oversamples of Puerto Rican, Cuban, and high income African American youth, as well as physically disabled youth, are planned to permit investigators to examine the determinants of health and measure health behavior within groups.

The researchers in this Study have gone to extraordinary lengths to assure that no one -- not even the study director -- can link the name of a participating individual or school with the information provided. Privacy will be enhanced by the use of computer technology that allows the adolescent to enter responses to questions directly into a laptop computer instead of telling them to an interviewer. Add HEALTH will obtain special federal protection to shield the data even from court subpoena or court order.

Mr. Porter: Why do you consider this survey to be so important? What kinds of research questions will it answer?

Dr. Alexander: This study is particularly important because it is the first comprehensive, nationwide study of the factors that affect adolescent health and well-being that examines a comprehensive range of health outcomes and health determinants at the individual, family, peer group, school, and community level.

While we all recognize the importance of these external influences on adolescent health and behavior, no national study before has ever been designed to measure their effects. This is important because an understanding of these influences will provide the scientific basis needed to inform and guide policy and program interventions to improve adolescent health. As an example, the adolescent health study will enable scientists to compare the effects on teenage smoking of: school curricula that discourage smoking, school smoking policies, local ordinances governing sale and advertising of tobacco products, parental smoking, and smoking by peers and close friends.

Knowledge of the relative importance of these sources of influence will help to effectively and efficiently target intervention efforts in an era of scarce resources.

The results of the adolescent health study will:

- help adolescents, parents, educators, and health care workers understand the factors that push young people into health-risking behaviors, and the factors that protect them;
- point the way to more effective interventions, by learning what kinds of interventions are likely to work best for which groups of teens, and by identifying protective factors at the family, school, and community level that may lead to new interventions;
- guide the delivery of services to adolescents, helping us better understand what services adolescents need and how to improve their ability to get them; and
- build a better scientific foundation for policies and programs designed to protect the health and well-being of our nation's young people.

VIOLENCE RESEARCH

Mr. Porter: With funding from the Office for Research on Minority Health, you are supporting a number of studies of community-based interventions to prevent violence. The Centers for Disease Control is also increasing its efforts in research on violence, and is testing community interventions as well. How is their research different from yours, and how do you coordinate your efforts?

Dr. Alexander: In late 1992, we initiated a set of cooperative agreements to develop, implement and evaluate community based health behavior interventions focusing on strategies for decreasing violence-related injuries and deaths, sexually transmitted diseases (STDs) and unwanted or unintended pregnancies in minority youth ages 10-18. The goals for these interventions reach beyond the delivery of information to help young people develop and practice skills in decision making, conflict resolution, and reducing their own risks of unhealthy outcomes. The projects involve collaborations among community-based groups and organizations and university-based researchers in both the design and the implementation and evaluation phases. These intervention studies differ from those sponsored by the Centers for Disease Control and Prevention by testing the effectiveness of interventions targeted at multiple risk behaviors. Informal coordination at the PHS level reinforced by coordination among programs at the local level (in sites where both CDC and NIH efforts are underway) have served to strengthen programs and avoid duplication. For example, one of the NIH investigators serves on the advisory board to a CDC intervention program, and this NIH investigator includes the CDC program officer on the advisory board of her program.

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Porter: Given that the Department of Veterans Affairs conducts a large amount of rehabilitation research, how has your Center carved out a niche for itself in the field?

Dr. Alexander: There are several features that distinguish research being supported by the National Center for Medical Rehabilitation Research (NCMRR) from rehabilitation-related research funded by the Department of Veterans Affairs (DVA). These are outlined below.

Research supported by NCMRR is relevant to all segments of the U.S. population with physical disabilities including infants and children and women of all ages. A defining characteristic of DVA research is that it must be relevant to the disabled veteran, among whom middle-age and elderly males predominate.

In addition, researchers supported by NCMRR are located in medical schools, universities, and free-standing research programs across this country. Principal investigators of DVA sponsored research are DVA employees situated in DVA medical centers. Additionally, NCMRR has mechanisms available to support research that are unavailable to DVA, an example being Small Business Innovation Research Grants which support the bulk of NCMRR research devoted to improving assistive technology for persons with disabilities. That funding mechanism is particularly useful for moving research innovations into the stages of manufacture and distribution.

Lastly, NCMRR emphasizes research areas relevant to people with disabilities for which DVA provides little or no support. One of those areas is the behavioral adaptation of people to living with disabilities. Another is outcomes research aimed at evaluating the effectiveness of specific rehabilitation practices. A third is research directed at preventing or controlling secondary health problems experienced by people with disabilities such as pressure sores, bladder and bowel dysfunction, and difficulties with reproduction. A fourth is research aimed at understanding the physiological and biochemical mechanisms underlying the chronic physical impairments which are the basis of physical disabilities.

SUDDEN INFANT DEATH SYNDROME

Mr. Stokes: In your opening statement, you say that between 1 to 12 months of life, sudden infant death syndrome is the single leading cause of death. In the United States, some 6,000 babies die each year from SIDS. You go on to say that last year, in some other countries, the rate of SIDS has dropped 50 percent or more following changes in sleep position, placing healthy babies on their back or sides to sleep to reduce the risk of SIDS. Do we know how much such success we have had with the sleeping position. Have we unraveled what else might cause SIDS, and additionally, what major research is underway at the Institute with regard to sudden infant death syndrome?

Dr. Alexander: It is too early to know whether the "Back to Sleep" message has had an impact on our SIDS rates. However there are scattered reports from a few states that the number of deaths from SIDS have dropped in 1994.

The Institute has developed, produced, and made available through the supported toll-free information line, 1-800-505-CRIB, the following materials:

- Brochures, "Reducing the Risk of Sudden Infant Death Syndrome: What You Can Do" (for caregivers) and "Questions and Answers for Professionals on Infant Sleep Position and SIDS;" a low-literacy parent brochure, with translation into Spanish, will be available by early spring of 1995;
- Bilingual (English/Spanish) take-home cards, and reminder stickers;
- Television, radio, and print public service announcements, and a SIDS risk-reduction video for parents;
- Posters in two versions, one featuring a white baby, and one featuring an African American baby.

The toll-free information line averages 3,000 calls per month. Several state public health departments and SIDS programs have ordered bulk quantities of educational materials in order to conduct state-wide education campaigns. More than 2,500,000 brochures have been distributed.

The Institute completed "Back to Sleep" mailings to 38,000 members of the American Academy of Pediatrics, 34,000 members of the American College of Obstetricians and Gynecologists, and 4,000 hospitals in the United States with newborn nurseries.

The TV public service announcement has played 16,000 times over the last nine months with national distribution, and two columns developed for local audiences have appeared in over 1,000 newspapers in 35 states reaching a potential readership of over 35,000,000.

Research studies have highlighted that many infants destined to die of SIDS have a range of abnormalities at birth that point to developmental delay or pathology in the regions of the central nervous system that control the coordination of arousal, heart rate, and breathing during sleep. This may be the reason that sleeping on the stomach, particularly on soft bedding, places them at greater risk for SIDS. A baby born to a mother who smokes while pregnant and after birth is at greater risk.

There is a multi-faceted, coordinated research program on SIDS at the Institute that grew out of the SIDS Five Year Research Plan. The major initiatives include:

- research and surveillance activities to determine the impact of the "Back to Sleep" message on health care provider advice, caregiver practices, and SIDS rates and other health outcomes;
- development and testing of new home monitoring technologies for infants at risk for SIDS;
- development and assessment technologies and physiologic tests to identify infants at risk for life-threatening episodes;
- case control epidemiologic studies in high risk urban and rural communities to determine the medical, environmental, and behavioral factors that are responsible for the high rates of sudden infant deaths in these communities; and
- basic research in animal models to understand the disease processes leading to SIDS.

Mr. Stokes: I understand that the Institute has developed a second five year plan for Sudden Infant Death Syndrome research (SIDS). Was the first five year research plan helpful to your efforts in this area, and if so, what were some of the accomplishments that resulted, and what are some of the opportunities now before us?

Dr. Alexander: The first SIDS research plan has made a significant difference in the SIDS research program of the NICHD. It provided guidance for the development and implementation of initiatives that covered a broad range of scientific, technological, clinical, and public health approaches to SIDS. Although most of the studies or programs funded under the five year plan are still in progress, some important accomplishments have been made:

- an updated definition of SIDS, and guidelines for death scene investigations have been developed under NICHD leadership to improve and standardize the diagnosis of sudden infant deaths throughout the United States;
- establishment of two brain and tissue banks for developmental disorders to increase availability of defined tissue specimens, encouraging high risk pilot investigations and testing of new hypotheses regarding SIDS;
- elucidation of brain abnormalities in SIDS infants that may make them vulnerable because they may not respond appropriately to hypoxia (low oxygen) or hypercarbia (elevated carbon dioxide) during sleep;

- development of animal models to assess the causes of sudden infant death;
- development of a partnership between the Northern Plains tribes and the U.S. Public Health Service to improve surveillance and prevention of sudden infant deaths in Native Americans;
- development of a new infant monitor for the home in collaboration with industry;
- elucidation of the properties of soft bedding that place an infant at risk for sudden death; and
- establishment of functional networks of researchers and policy makers, dedicated to reducing infant mortality.

The strong and organized SIDS research program that grew out of the SIDS research plan has provided us with the knowledge and resources to respond rapidly to new information. The opportunities for the future include:

- An unprecedented breakthrough has been made in SIDS prevention with back or side sleep position. Every opportunity should be taken to facilitate and advance the "Back to Sleep" campaign including designing and implementing interventions for "high risk" populations. National and overseas experience indicates that "high risk" populations are the most difficult to influence;
- Improve the effectiveness of preventive interventions by elucidating the interaction and mechanisms of environmental, cultural, and biological factors that mediate the risk conferred by prone sleeping;
- Sleeping on back or side has not eliminated SIDS and studies must be pursued to assess other factors such as maternal cigarette smoking;
- Some physiologic tests show promise to identify infants at risk for sudden death and must be tested for efficacy in large populations;
- Refine home monitoring technology to improve diagnostic capabilities and ease of use in the home; and
- Studies of brain abnormalities in SIDS infants must continue in order to clarify their role in SIDS and determine if detection and prevention measures can be developed.

VACCINE

Mr. Stokes: According to the Congressional Justification, the Institute has had tremendous success in the development of vaccines. The hemophilus influenza vaccine developed by the Institute is now part of the recommended routine childhood immunization series. Now the Institute has developed a safe and effective pertussis vaccine.

What major vaccine research and development initiatives are on the horizon? Among those which are ready to be exploited, how much is included in the FY 1996 budget request? How does this level of funding compare with the FY 1995 and FY 1994 funding level?

Dr. Alexander: The Institute has several very promising vaccine development initiatives on the horizon. Among these are:

- NICHD researchers have developed a vaccine against *Cryptococcus neoformans*, an organism that causes a life-threatening meningoencephalitis in approximately 8 percent of patients with AIDS. Phase II clinical trials are underway testing this new vaccine.
- There now are no licensed vaccines against the common and serious intestinal pathogens, *Shigella sonnei* and *Shigella flexneri*, which remain major causes of morbidity among children throughout the world. NICHD scientists have synthesized three shigella conjugates that have been shown to be safe and elicit serum antibodies in adults. In collaboration with scientists at the Walter Reed Army Institute of Research and the Israel Armed Forces, NICHD scientists have shown that one injection of their *S.sonnei* conjugate vaccine conferred a degree of protection against diarrhea and dysentry in army recruits caused by this pathogen. With the collaboration of the University of Chile, NICHD researchers are now studying the *Shigella flexneri* conjugate and *S. sonnei* conjugate in school-aged children and infants.
- NICHD investigators are using the novel conjugate technology, which they developed and which was so successfully utilized for the *Haemophilus* type b meningitis vaccine, to create vaccines against bacillary dysentery, cholera, and hospital-acquired bacteremia.
- Institute scientists are planning clinical trials to test the effectiveness of a new typhoid vaccine for infants and children under age two.
- Studies are in progress to permit testing a NICHD Group B strep/tetanus toxoid conjugate vaccine to prevent newborn Group B strep sepsis.
- An NICHD developed vaccine against E. coli 0157 has demonstrated success in producing high levels of antibody, and plans are under development for its further testing.
- NICHD scientists also are attempting to use the capsular polysaccharides of *Mycobacterium tuberculosis* to produce a new conjugate vaccine for pulmonary tuberculosis (TB).

The FY 1996 budget request includes $7,300,000 for vaccine research. This compares to $7,100,000 in the FY 1995 estimate and $6,937,000 in FY 1994.

BIRTH DEFECTS

Mr. Stokes: What is the extent of birth defects in the United States, and what is the cost to the Nation? Are we making very much progress in preventing and reducing birth defects?

Dr. Alexander: In the United States, 100,000 to 150,000 babies are born each year with a major birth defect. Of these babies, 6,000 die during their first 28 days of life, and another 2,000 will die before reaching their first birthday. Those who survive are affected in many ways by their birth defects. For example, children with birth defects account for about 25 percent to 30 percent of pediatric hospital admissions. Total costs for care of children with birth defects are very high.

Basic genetic and molecular studies have led to a number of important and exciting findings directed at understanding normal development and underlying mechanisms associated with birth defects. These include: the identification of some genes causing birth defects; development of new animal models; and the first application of gene therapy to treat successfully two children with severe combined immunodeficiency. In addition, the roles of environmental agents and nutritional factors are being studied.

A research team led by an NICHD investigator has identified a metabolic defect that may be responsible for a large number of neural tube defects (NTDs) such as spina bifida. This finding would explain the recent discovery that women who take folic acid prior to pregnancy or very early in pregnancy can dramatically reduce their risk of having a child with a NTD. Their study also suggests that the metabolic defect may be correctable with vitamin B12 as well as folic acid.

Another advance has been made with regard to preventing birth defects in the babies of women with phenylketonuria, an inborn error of amino acid metabolism. Women with phenylketonuria, who remain on a regular diet during pregnancy, have a high risk of giving birth to babies with small heads, mental retardation, congenital heart defects, and low birth weight. It has been found in an NICHD clinical trial that when placed on a special diet that contains low levels of phenylalanine before or early in their pregnancy, babies born to mothers who have kept their phenylalanine levels between 2 and 6 mg/dL, have improved reproductive outcome based on weight, length, head measurements, and cognitive function.

CHILDREN'S HEALTH

Mr. Stokes: Most often we hear so much about the 10 leading causes of death in general, what are the ten most life threatening health problems in children? How much of the Institute's budget is invested in each of these areas?

Dr. Alexander: Because of the major costs to society, I have focused my response on the leading causes of death during the first year of life. Specifically, in the United States for the year 1991--the last year for which we have complete data--the ten leading causes of infant (up to age one) death and estimates of the

Institute's FY 1994 expenditures on each cause are provided in the following table:

(Dollars in Thousands)

	Leading Causes of Death	FY 1994 Expenditures
1)	Congenital anomalies	$47,473
2)	Sudden Infant Death Syndrome (SIDS), Specific	10,766
3)	Disorders relating to short gestation and unspecified low birth weight	57,918
4)	Respiratory Distress Syndrome (RDS)	1,328
5)	Newborn affected by maternal complications of pregnancy	9,724
6)	Newborn affected by complications of placenta, cord, and membranes	342
7)	Accidents and adverse effects	1,934
8)	Infections specific to the perinatal period	31,543
9)	Pneumonia and influenza	842
10)	Intrauterine hypoxia and birth asphyxia	10,987

Mr. Stokes: In general, what is the state of children's health in the United States, and what is it for minority children?

Dr. Alexander: The health profile of American children has shifted markedly in the 32 years since NICHD was established. Once dominated by the threat of major infectious diseases, such as polio, diphtheria, scarlet fever, meningitis, pneumonia, measles, and whooping cough, today, widespread immunization has virtually eliminated many of these diseases. Others are in steep decline. In just the last 18 years, the rate of childhood deaths has declined 21 percent. Replacing infectious diseases are injury-related morbidity and mortality. Unintentional injuries are currently the leading cause of death in childhood. Nearly half of all childhood deaths are the result of unintentional injuries, and about half of these are due to motor vehicle accidents. Unintentional injuries are often preventable, and the rates of childhood deaths in motor vehicle crashes have decreased substantially as a result of prevention strategies of the last decade. Other causes of injury-related deaths among children--drowning, falls, poisoning, fires--have also declined as a result of improved protection, with the sole exception of child homicide.

Violence against children has become of increasing concern as an American health issue, with rapidly rising rates of reported cases of child deaths due to violence. Psychological, emotional, and learning disorders are on the rise among children, as are chronic physical conditions such as hearing and speech impairment. Low-income children are at a significantly higher risk for such problems. An accurate profile of the health of children in the U.S., therefore, must go beyond mortality and morbidity data. It must consider emotional, psychological, and learning problems, the social and environmental risks to which they are related, and the total costs to the Nation.

Unfortunately, Mr. Stokes, virtually all major health problems in children disproportionately affect minority children. For example, the infant mortality rate for black infants continues to be twice that of white infants. Black women are twice as likely as white women to experience prematurity, low birth weight, and infant and fetal death. The rates of fetal alcohol syndrome among American Indians/Alaska Natives is more than 30 times higher than for whites, and for blacks it is 7 times higher. The NICHD will continue to focus special attention on the health problems of minorities in its efforts to improve the health of all of our children and youth.

INFANT MORTALITY

Mr. Stokes: What is the current rate of infant mortality in the United States. To what extent have we seen an improvement in our infant mortality rate as compared to that of other countries? With respect to addressing this ongoing problem, what progress can you tell us this year that you could not tell us last year? How much is included in the FY 1996 budget request for this research area, and how does it compare with the FY 1995 and FY 1994 funding level?

Dr. Alexander: The latest figure for the Infant Mortality Rate (IMR), according to the National Center for Health Statistics, is for 1992 when it was 8.52 per 1,000 live births. The provisional rate for 1993 is 8.29 per 1,000 live births. The international ranking of the U.S. is most recently available for 1991. The U.S. ranks 24th which is unchanged from previous years.

A major research advance was recently made in the NICHD supported Newborn Intensive Care Network where it was demonstrated that corticosteroids administered to mothers in danger of going into premature labor resulted in a 50 to 60 percent reduction in their baby's risk of death or suffering complications such as brain hemorrhage, respiratory distress syndrome, and chronic lung disease. It is estimated that several thousand additional very low birth weight infants would survive each year if 60 percent of the mothers of preterm infants received antenatal steroids. Such use would result in a minimum savings of more than $150 million per year in the cost of hospitalization alone. Currently, it is estimated that fewer than 20 percent of mothers delivering prematurely receive antenatal steroids. The NICHD, based on the above findings, is actively joining with the American College of Obstetricians and Gynecologists, to promote the use of corticosteroids so that more infants may benefit from this preventive therapy.

The NICHD initiated, encouraged, and participated in a PHS initiative, the "Back to Sleep" campaign, to persuade parents and other caregivers of newborns to place healthy babies on their back or side to sleep to help reduce the risk of SIDS. The NICHD has developed, in conjunction with the American Academy of Pediatrics and other sponsors of the campaign, brochures for both parents and health care providers, posters, public service announcements, a 1-800 information telephone line, videos and other materials to promote the "Back to Sleep" campaign nationally. Although it is too early to know whether the "Back to Sleep" message has had an impact on SIDS rates, preliminary reports are encouraging.

The FY 1996 budget includes approximately $80,600,000 for research on infant mortality. This compares to $78,600,000 in the FY 1995 estimate and $76,405,000 in FY 1994.

Mr. Stokes: What progress has been made by your Institute's infant mortality initiative in the District of Columbia?

Dr. Alexander: As part of the District of Columbia Infant Mortality Initiative, a protocol has been developed and implemented for a randomized trial of an intensive intervention aimed at improving the parenting skills of high risk mothers. High risk in this case is defined as mothers who have inadequate or no prenatal care, which in turn is associated with poor utilization of infant health care services. Imparting essential parenting skills to high risk parents should result in improved utilization of preventive health services for young infants and children, as well as improved psychosocial development.

A study aimed at the prevention of childhood injuries has, as a first phase, developed a protocol for an injury surveillance program which is currently being implemented. Based upon the results of the surveillance, a specific intervention to lower both intentional and unintentional injuries in infants and children will be implemented.

Less than 50 percent of two year olds in the District of Columbia have completed their scheduled immunization. This lack of immunization not only reflects on the quality of infant and child health care in the DC but also places an unacceptable number of children at risk for preventable diseases. A study has been designed and is in the pilot phase to provide an assessment of determinants of incomplete immunization. It is planned to use the data from this assessment to develop coherent strategies for intervention and to test these interventions designed to improve immunization coverage among infants and children.

Another study will assess the impact of the neonatal services provided by the major hospitals in Washington, DC on the infant mortality rates in the District of Columbia.

Adolescent pregnancies are all too common and occur in the ecological context of poverty, stress and family dissolution. Such pregnancies are frequently followed by poor outcomes in subsequent pregnancies and a perpetuation of poverty. As part of this initiative an intervention aimed at the prevention of adolescent pregnancy, which is both school and clinic based, will be implemented in Washington, DC during the course of this year. The program is targeted to change knowledge, attitudes and behaviors of adolescent males and females.

MINORITY HEALTH

Mr. Stokes: Please briefly describe some of the other major achievements of your Institute's research in the last five years, especially those advances that have benefitted minorities.

Dr. Alexander: The following major achievements of NICHD research in the last five years especially have been beneficial to minority groups:

- The development of surfactant replacement treatment to prevent or cure Respiratory Distress Syndrome (RDS). This disorder was the leading killer of premature infants. Indeed, shortly before President Kennedy established the NICHD in 1963, his infant son died of RDS. At that time, the survival rate for a premature infant with RDS was less than 5 percent. With surfactant replacement treatment, the survival rate today has reversed to better than 95 percent.

- The development of a conjugate vaccine against *Hemophilus influenza* type b meningitis (Hib). This disease affected 15,000 children annually in the U.S., and was the leading cause of acquired mental retardation and a major cause of deafness. The NICHD Hib vaccine has reduced this disease by over 90 percent, and probably will eliminate it in the next few years, while saving as much as $460 million annually in health care costs.

- The NICHD sponsored the Consensus Development Conference that showed that antenatal steroids provide a rare example of a new medical treatment that not only keeps premature infants alive but yields cost savings as well. Research showed that use of these drugs significantly reduces mortality among preterm infants. The conference found that if the average rate of antenatal steroid use for premature births was increased from just 15 percent to 60 percent, the Nation could save $157 million in annual hospital and physician expenditures.

Mr. Stokes: What are some of the most exciting and promising clinical research opportunities that you plan to focus on in the near future; and how might these studies improve minority health?

Dr. Alexander: The Institute has a number of exciting and promising clinical research opportunities that it plans to pursue in the near future. A few examples include:

- A randomized, placebo-controlled Phase III clinical trial of metronidazole to prevent preterm birth in women with bacterial vaginosis or trichomoniasis. This condition disproportionately affects minority women, whose health would be improved by such a preventive treatment.

- In collaboration with the University of Chile, NICHD intramural scientists are studying two *Shigella* conjugate vaccines in school aged children and infants. *Shigella* infections remain a major cause of serious illness among children throughout the world, especially the disadvantaged living in unsanitary conditions.

- Phase II and III randomized comparative clinical trials of Zidovudine alone or Zidovudine/Nevirapine combination in pregnant HIV-infected women for the prevention of mother-to-child transmission of the infection. Because HIV/AIDS has a higher incidence among minority groups, this trial could be of significant benefit to infected minority women and their offspring.

VITAMIN RESEARCH

Mr. Stokes: According to the Justification, the Institute's supported research suggests that the metabolic defect is correctable with vitamin b-12. The Fogarty center during its hearing mentioned that vitamin-A is being used in the treatment of AIDS, in foreign countries. At your Institute, what other major studies are underway with respect to the use of vitamins as a treatment for disease?

Dr. Alexander: The NICHD is involved in a number of studies regarding the use of vitamins as a treatment for disease. These are outlined below.

Folate and Neural Tube Defects

Supplementation of the diet during pregnancy with folate has been shown in several large studies to reduce the incidence of neural tube defects in the offspring. The NICHD is conducting studies on folate metabolism in collaboration with the Health Research Board and Trinity College, Ireland. These investigations are designed to determine the biochemical mechanisms by which folate reduces the risk for neural tube defects. Data and blood samples have been collected on a large proportion of Irish women delivering babies in Dublin. Samples from women whose pregnancy ended in the delivery of a child with a neural tube defect and control women whose pregnancy ended in the delivery of a normal child are being studied. Various aspects of folate metabolism and other nutritional measures are being examined.

Folate Supplementation During Pregnancy

In view of the importance of adequate maternal levels of folate on the gross organization of the fetal brain and spinal cord it is important to study the impact of folate supplementation during pregnancy on more subtle measures of brain function later in childhood. Therefore, the NICHD is currently supporting a major study of the effects of folate supplementation during pregnancy on the neurodevelopmental status of the children of 930 predominantly African-American women when those children reach age 5. The children are now age 3, so results of this study will not be available for two more years.

Vitamin Supplements and AIDS

NICHD is currently funding several studies that are HIV-related and involve the use of vitamins in preventing the transmission of

HIV from mother to child (the principal source of pediatric infection) or the prevention of progression of HIV infection in children already infected by HIV. Two studies (one in Malawi and one in Tanzania) focus on whether or not treatment with vitamin A can prevent the transmission of HIV from infected pregnant women to their offspring. A third study in Uganda looks at whether or not treatment of infected children with vitamin A improves their overall outcome with respect to morbidity and mortality. Some of the importance of these studies lies in the fact that vitamin A costs a few pennies to administer while agents like AZT can cost thousands of dollars per patient. In order to determine whether or not vitamin A affects the health of HIV-infected children in the U.S., we are evaluating stored serum samples from one of our earliest AIDS studies in children. Similarly, we are planning to test for vitamin A levels in samples taken from HIV-infected pregnant women in another of our studies. The results from these latter two efforts will indicate whether or not vitamin A assessment and treatment are important issues to consider in the U.S. maternal and child population afflicted by HIV/AIDS.

Vitamin A Deficiency

Recent epidemiologic studies have shown that children with marginal vitamin A deficiency (VAD) are at increased risk of developing and dying from measles and other respiratory and enteric infections. The secretory immunoglobulin system plays an important role in protecting against such infections. VAD may increase susceptibility to mucosal infections by decreasing production of secretory immunoglobulin or impairing its transport across epithelial surfaces. For these reasons NICHD-supported scientists are examining the effect of vitamin A on the secretory immunoglobulin response in a mouse model. Investigators will determine if VAD affects the mucosal response to intranasal infection with influenza A virus.

Vitamin A and Reproduction

Vitamin A is known to play an important role in the growth and maintenance of cells and tissues throughout the body. In particular, the role of this vitamin is of importance in maintaining the health of the human male reproductive system. The goal of this research is to understand the essential role that vitamin A plays in male reproductive function and its metabolism in the testis and epididymis. This research seeks to clarify the roles of several specific transport or binding proteins for vitamin A in these organs.

Basic Research:

In addition to studies of vitamins and disease, the NICHD funds basic research on how vitamins influence the growth and development of embryonic and fetal tissues in animal models and in tissue culture. This research may elucidate the earliest origins of congenital defects and provide clues for their prevention with vitamins.

Retinoic Acid in Early Embryogenesis

Retinoic acid, a form of vitamin A, is known to affect cell differentiation, proliferation, and pattern formation. The actions of retinoic acid are mediated through retinoic acid receptors. The long-term objective of this project is to understand the roles of retinoic acid and its receptors in early pregnancy in a mouse model. These studies should reveal the molecular mechanisms by which retinoic acid and its receptors regulate embryogenesis, cell differentiation, and gene expression.

Retinoid-Binding Proteins in Embryogenesis

Vitamin A and retinoic acid regulate many aspects of cell growth and differentiation, and thereby play an important role in vertebrate morphogenesis. In mammals, retinoids are well known to be potent teratogens in both deficiency and excess, with the developing nervous system being a primary target. NICHD-supported research is aimed at defining the role of retinol binding proteins in the regulation of gene expression during vertebrate development. The goal of this study is to delete the retinol binding protein function in cell lines through gene targeting technologies. These cells lines can be used to generate mutant mice with no retinol binding protein. Analysis of the development of these mice will establish if retinol binding proteins are essential for normal embryo development.

Retinoids in Vertebrate Development

This research explores the role of retinoic acid in vertebrate development and is important for understanding the physiologic role of retinoic acid in limb development. Although this study centers on the role of retinoids in vertebrate limbs, the resulting information will increase our general understanding of this important class of vitamins which control the flow of intracellular information and gene expression.

Role of Vitamin D in Skeletal Growth

Vitamin D is important for skeletal growth but the mechanism by which it affects this process is poorly understood. NICHD-supported scientists have obtained evidence from chicken limb bud cells in tissue culture suggesting that vitamin D plays an important role in cartilage formation. This evidence helps to explain the mechanisms by which vitamin D deficiency causes rickets. Investigators will identify vitamin D genes necessary for the initiation of cartilage differentiation. Knowledge gained from these studies will be important in understanding skeletal development and may be applicable to congenital abnormalities of human skeletal development.

OPPORTUNITIES

Mr. Stokes: Please describe the most promising opportunities in basic as well as clinical research you see for your Institute in the next several years, and elaborate on the benefits that could be derived from investments in these areas.

Dr. Alexander: Vaccine development continues to be one of the Institute's most promising areas of scientific opportunity. Emerging new conjugate technology has raised the possibility of developing vaccines to prevent many of the remaining common childhood infections. Investments in the prevention of disease, especially at an early stage in life, have produced significant savings, both in terms of financial costs and the costs of suffering and lost productivity, perhaps for a lifetime.

Another promising scientific opportunity the Institute plans to pursue is the further study of folic acid, which our research has shown decreases the risk of having an offspring with spina bifida or other neural tube defect. The prevention of neural tube defects would significantly decrease life-long morbidity and disability.

Promising opportunities in research also exist in the field of AIDS prevention. Recent success in preventing the maternal transmission of AIDS demonstrated by the ACTG 076 Clinical Trial has laid the groundwork for NICHD/NIAID-supported follow-up studies to determine the long-term effects of the intervention. Investing in this area will help advance efforts to prevent the transmission of AIDS, especially among women, adolescents and infants.

Especially promising lines of investigation for support by the Institute's National Center for Medical Rehabilitation Research (NCMRR) include: 1) using advances in biocompatible materials and aerospace manufacturing techniques to develop improved assistive technology (e.g. prostheses, orthoses, and environmental controls) to enhance the independence and productivity of persons with physical disabilities; 2) developing more effective healthcare practices to prevent or control health problems such as chronic pain or new muscle weakness that are prevalent among people with spinal cord injury, post-polio syndrome, and cerebral palsy; and 3) evaluating the effectiveness of existing medical rehabilitation practices in order to improve outcomes and control costs.

Finally, the Institute plans to continue pursuing promising scientific opportunities in research to develop: safe, new contraceptive products for both men and women, more effective methods for treating male and female infertility at reduced costs, approaches for determining what factors play a role in fertility, and programs for understanding fertility-related behavior.

13 Mr. Stokes: To what extent will the FY 1996 budget allow the Institute to begin to implement the opportunities that are ready to be exploited?

Dr. Alexander: The FY 1996 request, which provides an overall 3.1 percent increase over FY 1995, will enable the NICHD to address our highest priorities. Of the amount requested, $5,786,000 has been targeted towards special areas of emphasis which highlight NIH and PHS initiatives for FY 1996. These initiatives include disorders of developmental and reproductive biology, gene therapy, prevention, and breast cancer research. Research in these emphasis areas cut across all of the NICHD's major program activities including infant mortality and child health, reproductive health/contraceptive development, medical rehabilitation research, and pediatric AIDS.

VIOLENCE

Mr. Stokes: According to the Congressional Justification, research supported by your Institute provides the basis for developing and evaluating intervention programs to reduce violence and related behaviors in youth. What major initiatives are underway and planned for FY 1996?

Dr. Alexander: With funding from the NIH Office for Research on Minority Health, NICHD supports a set of eight cooperative agreements to develop, implement, and evaluate coordinated programs of community based health behavior interventions designed to focus on strategies for decreasing violence-related injuries and death, sexually transmitted diseases (STDs) and unwanted or unintended pregnancies in minority youth ages 10-18. These initiatives will continue in FY 1996.

Mr. Stokes: What research is the Institute doing on the problem of violence among our youth?

Dr. Alexander: As described in the previous answer, the NICHD initiated a set of cooperative agreements to develop, implement and evaluate community based health behavior interventions in minority youth. The goals for these interventions reach beyond the delivery of information to help young people develop and practice skills in decision making, conflict resolution, and reducing their own risks of unhealthy outcomes. The projects involve collaborations between community-based groups and organizations and university-based researchers in both the design and the implementation phases. The Office of Research on Minority Health is providing the funding for this NIH initiative and the National Institute of Child Health and Human Development (NICHD) is managing the 5-year program.

AIDS

Mr. Stokes: Last year, you reported to the Committee on the success of AZT in reducing the transmission of the AIDS virus from HIV-infected women to their babies. It has just been reported that a child born with AIDS five years ago is now showing no signs of the disease. It appears as though the child's immune system fought off the disease. What hope does this offer for furthering research that is geared toward a cure for this disease? Would you bring the Committee up-to-date on the Institute's AIDS research initiative?

Dr. Alexander: NIH funded researchers at UCLA reported in the New England Journal of Medicine the case of an infant who was exposed to HIV through the birth process, had well-documented laboratory evidence of infection early on, then appears to have become uninfected on his own and remains well at 5 years of age. This case suggests that the body's immune system may be capable in some instances of "clearing" HIV once infection has occurred. In this case, not only is there no evidence of disease, there is no evidence of persistent latent (hidden) infection. Whether this case represents (a) complete elimination of HIV infection by an immune mechanism, (b) containment with total suppression of HIV by an immune mechanism, or (c) the virus dying off on its own is not yet clear. The UCLA researchers are still studying what immune mechanism(s) may have been involved. In most communicable diseases, not everyone who is exposed becomes infected, and not everyone who is infected gets sick. HIV is unusual in that almost everyone who is infected eventually gets sick.

Most (about 3 out of every 4) infants born to HIV-infected women do not become infected. Recent advances in laboratory diagnosis have made it possible to tell which infants are infected and which infants are not infected much sooner after birth than in the past.

Most infants who eventually are shown to be uninfected never show any evidence that they were infected at any point, although they are not usually studied as extensively as in the UCLA case. What the UCLA researchers have reported is important because it suggests that in some (probably the minority) of cases, it is possible for a newborn to be exposed to HIV, for HIV infection to occur, and for the infection to be cleared by an immune mechanism.

Studying when and how immune clearance of HIV occurs is of enormous potential value for vaccine development and other treatment research. If natural mechanisms of defense can be invoked or mimicked, this holds great promise for developing methods of preventive treatment for exposed persons and even the possibility of virtually curative treatment for infected persons. Research on HIV infected women and their infants is critical because it is perhaps the one area where transmission of HIV can be studied best and is the most likely to yield clues that will advance vaccine development and other preventive or curative treatment research.

A number of NICHD supported studies are evaluating the factors and mechanisms that either increase or protect against transmission of HIV in infants born to infected women. The Women and Infants Transmission Study, a project jointly sponsored by NICHD and NIAID, currently is evaluating the circumstances wherein and the mechanisms whereby infection occurs and does not occur.

Researchers supported by NICHD, NIAID, and other Institutes of NIH are developing interventions based on active and passive immunization to prevent infected pregnant women from transmitting HIV to their children. This approach is analogous to the highly successful strategy to prevent hepatitis B in newborns, which uses a combination of hyperimmune globulin (a protein solution containing high concentrations of antibodies to hepatitis B) given at birth and a series of vaccinations given at birth and during infancy. Currently, Phase I studies are evaluating the ability of available candidate HIV vaccines to stimulate immune responses in HIV-infected pregnant women and in their infants. The NIH also supports efficacy trials in the United States and other countries to evaluate passive immunization for the prevention of perinatal transmission.

Mr. Stokes: What is the most significant AIDS research that is underway at your Institute? To what extent has knowledge gained in AIDS research and breast cancer research had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your Institute?

Dr. Alexander: One of the major components of AIDS research at NICHD is the evaluation of new agents for prevention and treatment of HIV infection itself as well as its complications in children, adolescents and women. To ensure the most cost-efficient use of federal dollars for research, NICHD conducts most of its clinical trials in collaboration with the Pediatric AIDS Clinical Trials Group funded by NIAID.

One of the major achievements of this collaborative effort was the results of a 1994 clinical trial (ACTG 076) demonstrating that administration of AZT to pregnant women and their newborns can reduce the risk of transmission of HIV from mother-to-child by two-thirds. Another important achievement was a trial that found that monthly administration of intravenous immunoglobulin (IVIG) to HIV-infected children significantly reduced bacterial and viral infections and hospitalizations. In 1994, the FDA provided a labeling indication for use of IVIG for this purpose based on the results of this trial.

The results of ACTG 076 had great public health importance and implications. Within a month of the announcement of the trial results in February 1994, the Public Health Service set up an Interagency Task Force, which was headed by an NICHD medical officer. The Task Force was given the charge to develop treatment recommendations for the use of AZT to reduce transmission (published in August 1994), review and revise recommendations for HIV counseling and testing in pregnant women (published in the Federal Register for public comment in February 1995), and facilitate relevant activities in other agencies. For example, FDA granted a labeling indication for AZT for reducing perinatal transmission in July 1994 and AHCPR is currently in the process of finalizing an educational brochure to assist women in their decision-making about using AZT for this purpose.

This ground-breaking study has spurred efforts at NICHD to develop other methods to reduce perinatal HIV transmission. NICHD is funding a study, in collaboration with NHLBI and NIAID, evaluating passive immunization with an immunoglobulin preparation of concentrated HIV antibodies (hyperimmune HIV immunoglobulin) in combination with AZT to reduce mother-to-child transmission in infected pregnant women with advanced HIV disease. NICHD is also funding a study in Africa to evaluate the potential use of vitamin A and multivitamin supplementation of infected pregnant women to reduce perinatal transmission.

Because it is now clear that prevention of infection is possible, efforts at the development of modalities for prevention of sexual transmission of HIV are also underway at NICHD through funding the development of barrier contraceptives including virucidal vaginal microbicides. The NICHD is using its biologic testing facility to hasten product testing and is establishing a multicenter network to test rapidly both chemical and physical barriers. This involves testing new formulations for nonoxonyl-9, new spermicides with microbicidal properties, novel vaginal products that can maintain the vaginal ecosystem, new physical barriers for women and nonlatex male condoms. The NICHD is also working with the FDA and others to evaluate and improve the labeling of contraceptive agents regarding prevention of STDs, develop new rules for approving spermicidal compounds, and improve the design of clinical trials testing dual-purpose products.

It has been known that spermicides reduce the spread of STDs but the new focus on microbicidal development is enabling us to define the effectiveness of the various formulations. Vaginal irritation when spermicides are used has been a major concern, but little information as to the amount of irritation has been available. In addition, studies in monkey models will provide information as to how important irritation is in the spread of AIDS.

The most significant AIDS research now underway supported in the area of contraceptive evaluation is a prospective observational study of the effectiveness of the female condom in prevention of sexually transmitted diseases (STDs) including HIV. This study will compare the female condom to male condoms, when used either with or without spermicides. Since comparative clinical trials have never been conducted to assess the relative efficacy of the various barrier contraceptives, this study will make more informed choices of contraceptive methods possible and will reduce the uncertainty concerning efficacy that leads some to avoid an otherwise effective method.

The NICHD's research on breast cancer focuses on the connection between breast cancer and oral contraceptives. Findings from research in this area would have implications in the area of contraceptive development and reproductive medicine, and will allow for more informed choices in the selection of contraceptive methods.

NEUROLOGICAL AND BEHAVIORAL RESEARCH

Mr. Stokes: A few weeks ago, the Committee had the opportunity to hear testimony from the Nation's Nobel Laureates. They indicated that neurological and behavioral research are among the most important areas that if enhanced -- offered considerable opportunity for improving human health.

For children, neurological disorders can mean a lifetime of disability. To what extent are we making advances in preventing neurological disorders in low birth weight infants and in children in general?

Dr. Alexander: Newborn screening programs to detect a number of genetic abnormalities including phenylketonuria, galactosemia, and congenital hypothyroidism, have resulted in the early detection and treatment of these abnormalities resulting in the prevention or amelioration of morbidity associated with these conditions.

In the area of diagnostic imaging, new technologies, particularly functional MRI, are providing the capability to test children on tasks that relate to their language and attentional capacities. These techniques allow scientists and clinicians to characterize which brain areas are involved in reading and attention. Such advances could provide neuropsychologists and child neurologists with better approaches for making diagnoses and assessing treatments for learning disabilities and attention deficit disorders. The Institute sponsored a conference on developmental neuroimaging approaches in January of 1994. A book based on this meeting is in press.

Research is also being conducted to evaluate interventions aimed at reducing developmental and health problems of low-birth-weight premature infants. For example, in a clinical trial involving eight sites, infants were randomly assigned to receive an educational curriculum focused on child development, family support and pediatric follow-up or only pediatric follow-up. At 36 months of age, the intervention group had significantly higher mean IQ scores than the follow-up group. In addition, significantly fewer behavior problems, and a small, but statistically significant, increase in minor illnesses were reported by the mother, with no difference in serious health conditions. Follow-up evaluation of these children is being conducted to determine if the beneficial effects of early intervention will persist through school-age.

Mr. Stokes: We heard considerable testimony from Public Witnesses this year concerning brain disorders in children. How extensive is this problem? What opportunities are on the horizon and are ready to be exploited regarding the treatment and prevention of brain disorders in children?

Dr. Alexander: In the United States, neurological disease affects some 50 million people of all ages every year with childhood disorders representing a substantial portion of the total. About 2,000 genetic disorders have been described, more than half of which affect the nervous system. Brain damage from fetal alcohol exposure, Down syndrome, and the fragile X syndrome collectively affect well over 3 in 1000 live births. The incidence of epilepsy is 72-86 per 100,000 for children under 9 years of age; the incidence is highest among infants less than 1 year old. Cerebral palsy occurs in 1.5 to 2.0 per 1000 live births. As many as 6 million Americans are classified as mentally retarded. Newborn screening for genetic disorders followed by early treatment; public education about risks to the fetus from drugs, alcohol, and other harmful substances such as lead; better prenatal and child care; and systematic efforts to remove environmental toxins are but a few examples of public health programs that can result in the prevention of brain disorders in children.

One area of particular interest to the NICHD involves learning disability (LD). Approximately 18-20 percent of American children suffer from this problem. Recent progress has been made on one type of learning disability termed dyslexia, the inability to read. Institute-funded scientists have discovered that a basic capacity, phonological awareness, is impaired in the at-risk population of dyslexic children. They have a lessened ability to detect the sound units associated with the letters that make up words. Due to this problem they have difficulty in decoding the letter-sound relationships necessary for reading. Research from our LD centers has provided new ways to image the brain of such children so that the signatures of brain activity for reading can be determined. These techniques provide the opportunity to characterize brain activity pattern differences between normal readers and those who have difficulty. Other researchers sponsored by the Institute have learned that if children are not treated for this condition before the age of nine years (when they are typically tested in school for reading competence), they are likely to have reading difficulties for the rest of their lives. Studies currently under way, supported by the Institute, are employing techniques for early intervention, based on teaching phonological awareness. Such interventions should benefit both at-risk children and those who will learn how to read without difficulty. The new imaging technologies will be useful in evaluating whether brain signatures are improved for at-risk children who are taught phonological awareness early (at 4 years of age).

Mr. Stokes: What is the extent of the Institute's investment in this particular area of research in FY 1996? How does this compare with FY 1995 and 1994?

Dr. Alexander: The FY 1996 request provides approximately $57,700,000 for research pertinent to understanding processes involved in neurological disorders that affect infants and children and to preventing these disorders. The studies supported by NICHD encompass conditions that occur before birth such as congenital defects, during the birth process, and postnatally. The FY 1995 estimate and the FY 1994 amounts for research in this area are $56,000,000 and $54,367,000, respectively.

CHRONIC FATIGUE AND BLOOD PRESSURE

Mr. Stokes: I understand that researchers have identified a link between chronic fatigue and blood pressure in teenagers. How significant a research finding is this and what can you tell us about the implications of this research finding in furthering our understanding of both of these diseases?

Dr. Alexander: In a recently published paper (Lancet, volume 345, pps 623-24, March 11, 1995) investigators at Johns Hopkins University (Peter C. Rowe, Issam Bou-Hofalgah, Jean S Kan, Hugh Calkins) describe studies of seven consecutive teenagers whose primary complaint was fatigue and who had recurrent episodes of lightheadedness without fainting. Four of these teenagers met the 1988 criteria for chronic fatigue syndrome. When subjected to a protocol involving tilt-table testing, all developed clinically important hypotension (low-blood pressure) during the procedure.

After completion of the testing protocol, all were instructed to increase their salt intake and all were treated with a beta-blocker or disopyramide. Symptoms of lightheadedness and post-exertional fatigue resolved or substantially improved in four.

The significance of this finding as stated by the authors is that: "The abnormal responses to upright tilt-table testing in this series demonstrate that chronic fatigue can be part of the clinical spectrum of neurally mediated hypotension, even when patients have not experienced recurrent syncope" (fainting).

The implications of this research for chronic fatigue syndrome were indicated by the authors as follows: "Further studies are needed to assess the usefulness of the tilt-table test in those with chronic fatigue syndrome, and randomized trials are needed to assess whether drugs used for the treatment of neurally mediated hypotension will consistently improve the profound disruption of daily life in these individuals."

We understand that these investigators are planning such additional studies and tests.

RESEARCH PROJECT GRANTS

Mr. Stokes: For your Institute, if we examine five year increments, to what extent has the success rate remained relatively flat over the past five to ten years?

Dr. Alexander: The success rate is determined by dividing the number of applications funded by the number that is reviewed. Except for FY 1987 when a success rate of 33.2 was achieved, the period FY 1985 through FY 1989 experienced a relatively flat success rate of about 25 percent. In FY 1990, the success rate dropped to 19.3 percent and then rose again to a high of 26.3 percent in FY 1992. Since FY 1992, the success rate has steadily declined to a projected low of 17 percent in FY 1995.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period. What is the trend in terms of constant dollars?

Dr. Alexander: In current dollars, the average costs of competing grants has risen, for the most part steadily, from $136,900 in FY 1985 to $215,900 in FY 1995. This represents an increase of 57.7 percent over a ten year period or a yearly average increase of about 4.8 percent. In terms of constant dollars, using the Biomedical Research and Development Price Index as a deflator, the average cost increase over the 10 year period is about .8 percent or an average of less than .08 percent per year.

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From HBCUs?

Dr. Alexander: To comply with Federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NICHD is unable to identify accurately the number of applications submitted by minorities and women or the number of awards to minorities and women. In FY 1994, approximately 21 percent of grant applicants chose not to complete the portion of the grant application referring to race and 4 percent of applicants chose not to complete the portion referring to gender. These applicants have been coded in the "unknown" category. Since there is no way to predict the race or gender composition of these applicants, the data in the following table may not provide a true representation of NICHD's support of minority and women researchers.

FY 1994 Success Rates for Minority and Women Applicants

Applicant Pool	Number of Applications Received	Success Rate
Total Applicants	1,661	20.5%
All Minority Applicants	184	14.1%
African American Applicants	21	9.5%
Unknown	348	29.3%
Women	519	16.4%
Unknown	72	43.1%
HBCUs	4	--%

Mr. Stokes: For the same time period, in real and in constant dollars, what has been the average costs of research project grants awarded to women? to minority researchers? To HBCUs?

Dr. Alexander: As stated above all questions related to race and gender are identified as optional on all NIH research grant applications. As a result, NICHD is unable to identify accurately the number and amount of awards to minorities and women. Thus the following table may not accurately reflect a true representation of NICHDs support for minority and women researchers.

Average Competing Grant Costs for Minority and Women Researchers
(Dollars in thousands)

Applicant Pool	FY 1985 Average Cost Awarded	FY 1994 Average Costs Awarded Current $	FY 1994 Average Costs Awarded in FY 1985 Constant $
Total Awards	$136.9	$212.5	$141.3
All Minority	130.7	190.1	126.4
African American	369.0	246.7	164.0
Unknown race	151.8	216.6	144.0
Women	132.2	183.7	122.1
Unknown gender	51.2	264.3	175.7
HBCUs	484.6	---	---

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

FY 1996 Budget — Page No.

Organization chart 2

Appropriation language 3

Amounts available for obligation 5

Budget mechanism table 6

Summary of changes 8

Budget authority by object 10

Administrative costs 12

Significant items in House and Senate Appropriations Committee Reports 13

Authorizing legislation 19

Appropriation history 20

Budget authority by activity 22

Justification:

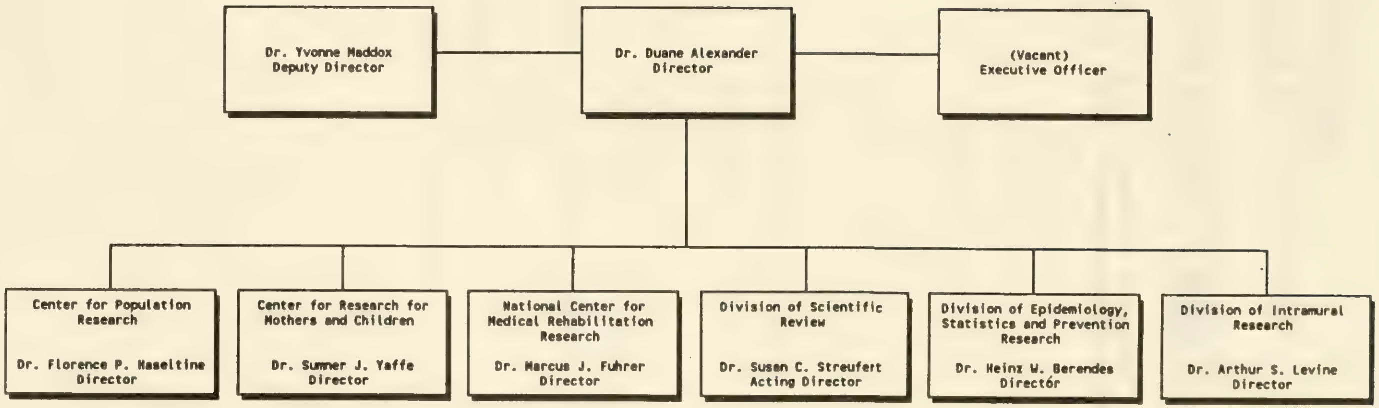
A. General statement 23
B. Extramural research 26
C. Intramural research 36
D. Research management and support 40
E. Detail of full-time equivalent employment (FTE) 41
F. Detail of end-of-year employment 42

2

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Organization Structure


Dr. Yvonne Maddox
Deputy Director
Dr. Duane Alexander
Director
(Vacant)
Executive Officer
Center for Population Research
Dr. Florence P. Haseltine
Director
Center for Research for Mothers and Children
Dr. Sumner J. Yaffe
Director
National Center for Medical Rehabilitation Research
Dr. Marcus J. Fuhrer
Director
Division of Scientific Review
Dr. Susan C. Streufert
Acting Director
Division of Epidemiology, Statistics and Prevention Research
Dr. Heinz W. Berendes
Director
Division of Intramural Research
Dr. Arthur S. Levine
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to child health and human development, [$513,409,000] *$526,177,000.*

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation...............	$555,195,000	$513,409,000	$526,177,000
Rescission in accordance with PL 103-211...........	-314,000		
Section 205 Procurement reduction.................		-242,000	
Section 207 Rent reduction..		-51,000	
Section 513 S&E reduction...		-264,000	
Subtotal, Adjusted Appropriation...........	554,881,000	512,852,000	526,177,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities..	-56,426,000		
Comparative transfer to: Other NIH Institutes for Management Fund adjustment.	-2,736,000	-2,696,000	
Subtotal, adjusted budget authority.........	495,719,000	510,156,000	526,177,000
Unobligated balance, lapsing....................	-45,000		
Total obligations........	495,674,000	510,156,000	526,177,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1994--$23,094,000; FY 1995--$19,258,000; FY 1996--$19,258,000.

Also excludes funding for HIV activities: FY 1995--$58,667,000; FY 1996--$60,713,000, included in the Office of AIDS Research, NIH.

Note: Excludes $70,000 in FY 1994 and $106,000 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research projects						
Noncompeting	920	$192,405,000	939	$214,331,000	884	$215,436,000
Admin. supplementals	(113)	6,255,000	(80)	3,900,000	(80)	3,900,000
Competing:						
Renewal	111	29,591,000	91	25,265,000	94	27,356,000
New	202	34,859,000	162	29,444,000	172	32,765,000
Supplemental	2	191,000	--	---	1	100,000
Subtotal, competing	315	64,641,000	253	54,709,000	267	60,221,000
Subtotal, res. proj	1,235	263,301,000	1,192	272,940,000	1,151	279,557,000
SBIR/STTR	48	7,536,000	56	8,614,000	56	8,842,000
Subtotal, res. proj	1,283	270,837,000	1,248	281,554,000	1,207	288,399,000
Research centers						
Specialized/comp. centers	77	47,519,000	78	46,837,000	78	48,282,000
Other research						
Research career program	96	7,686,000	96	7,775,000	96	8,000,000
Coop. clin. research	41	20,373,000	41	20,500,000	41	21,095,000
BRS	--	---	--	---	--	---
Minor. biomed. res. support	--	558,000	--	585,000	--	602,000
Other research related	46	2,296,000	46	3,109,000	46	3,200,000
Subtotal, other research	183	30,913,000	183	31,969,000	183	32,897,000
Total, research grants	1,543	349,269,000	1,509	360,360,000	1,468	369,578,000

Training						
Individual awards:						
Noncompeting.................	61	1,998,000	68	2,167,000	69	2,195,000
Competing....................	30	744,000	23	748,000	23	748,000
Subtotal, individ.........	91	2,742,000	91	2,915,000	92	2,943,000
Institutional awards:						
Noncompeting.................	520	11,704,000	519	11,939,000	520	12,047,000
Competing....................	114	2,645,000	138	3,269,000	138	3,269,000
Subtotal, inst............	634	14,349,000	657	15,208,000	658	15,316,000
Total, training.................	725	17,091,000	748	18,123,000	750	18,259,000
Research and development contracts....................	98	33,663,000	98	34,682,000	98	38,688,000
(SBIR/STTR)	(2)	(311)	(5)	(870)	(5)	(870)
	FTEs		FTEs		FTEs	
Intramural research.............	316	69,693,000	320	70,726,000	315	72,725,000
Research management and support......................	188	26,003,000	188	26,265,000	188	26,927,000
Total..........................	504	495,719,000	508	510,156,000	503	526,177,000
Clinical Trials.................		(47,310,000)		(48,400,000)		(50,000,000)

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes

1995 Estimated budget authority	$510,156,000
1996 Estimated budget authority	526,177,000
Net Change	+16,021,000

	1995 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$26,600,000		+$305,000
b. One more day of pay		26,600,000		+102,000
c. Annualization of January 1995 pay increase		26,600,000		+167,000
d. January 1996 pay increase		26,600,000		+609,000
e. Payment for centrally furnished services		17,482,000		+877,000
f. Service and supply fund increase		6,097,000		+177,000
g. Increased costs for services and supplies		20,297,000		+596,000
h. FTE reduction		26,600,000		-300,000
i. FTS reduction		250,000		-51,000
Subtotal				+2,482,000
2. Research Management and Support				
a. Within grade increase		$12,436,000		+143,000
b. One more day of pay		12,436,000		+48,000
c. Annualization of January 1995 pay increase		12,436,000		+69,000
d. January 1996 pay increase		12,436,000		+265,000
e. Federal employees compensation fund, unemployment compensation		129,000		+4,000
f. Payment for centrally furnished services		6,965,000		+253,000
g. Service and supply fund increase		3,794,000		+72,000
h. Increased costs for services and supplies		4,372,000		+127,000
i. FTE reduction		12,436,000		-200,000
j. Working capital fund decrease		449,000		-12,000
Subtotal				+769,000

Summary of Changes--continued

Changes:	1995 Current Estimate Base FTEs	1995 Current Estimate Base Budget Authority	Change from Base FTEs	Change from Base Budget Authority
B. Program:				
1. Research project grants:	No.	Amount	No.	Amount
a. Noncompeting...........	939	218,231,000	-55	+1,105,000
b. Competing..............	253	54,709,000	+14	+5,512,000
c. SBIR/STTR..............	56	8,614,000	---	+228,000
Total..................	1,248	281,554,000	-41	+6,845,000
2. Research centers	78	46,837,000	---	+1,445,000
3. Other research	183	31,969,000	---	+928,000
4. Research training	748	18,123,000	+2	+136,000
5. Research and development contracts.................	98	34,682,000	---	+4,006,000
	FTE		FTE	
6. Intramural research.........	320	70,726,000	-5	-483,000
7. Research management and support..................	188	26,265,000	---	-107,000
Subtotal................				+12,770,000
Total changes..................				+16,021,000

10

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Object

	1995 Appropriation	1996 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	508	503	-5
Full-time equivalent of overtime and holiday hours................	5	5	---
Average ES salary.....................	$106,600	$110,000	+$3,400
Average GM/GS grade...................	11.0	11.0	---
Average GM/GS salary..................	$47,800	$49,400	+$1,600
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)....................	$77,600	$80,100	+$2,500
Average salary of ungraded positions..	$24,000	$24,800	+$800
Personnel compensation:			
Full-time permanent................	$18,252,000	$18,954,000	+$702,000
Other than full-time permanent.....	6,454,000	6,661,000	+207,000
Other personnel compensation.......	1,357,000	1,400,000	+43,000
Special personnel service payments..	5,958,000	6,266,000	+308,000
Total personnel compensation....	32,021,000	33,281,000	+1,260,000
Personnel benefits....................	6,565,000	6,611,000	+46,000
Benefits for former personnel.........	200,000	206,000	+6,000

	1995 Appropriation	1996 Estimate	Increase or Decrease
Travel and transportation of persons...	1,108,000	1,119,000	+$11,000
Transportation of things...............	190,000	197,000	+7,000
Rental payment to GSA..................	16,000	17,000	+1,000
Rental payment to others...............	4,000	5,000	+1,000
Communications, utilities, and misc....	1,645,000	1,641,000	(4,000)
Printing and reproduction..............	988,000	1,016,000	+28,000
Other services:			
Consulting services.................	831,000	845,000	+14,000
Other Services......................	8,599,000	8,265,000	(334,000)
Purchases from Gov't Accounts.......	36,616,000	38,152,000	+1,536,000
R&D Contracts.......................	29,113,000	33,037,000	+3,924,000
Supplies and materials.................	7,594,000	7,676,000	+82,000
Equipment..............................	6,072,000	6,160,000	+88,000
Lands and structures...................	6,000	6,000	---
Grants, subsidies, & contributions.....	378,483,000	387,837,000	+9,354,000
Insurance Claims and Indemnities.......	105,000	106,000	+1,000
Total budget authority by object....	510,156,000	526,177,000	+16,021,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

12

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Administrative Costs

	1995 Current Estimate	1996 Estimate	Change
Personnel Compensation:			
Full-time permanent (11.1)..............	$18,252,000	$18,954,000	+$702,000
Other than Full-Time Permanent (11.3)...	6,454,000	6,661,000	+207,000
Other Personnel Compensation (11.5).....	1,357,000	1,400,000	+43,000
Special Personnel Serv. Payments (11.8).	5,958,000	6,266,000	+308,000
Total Personnel Compensation (11.9)...	32,021,000	33,281,000	+1,260,000
Civilian Personnel Benefits (12.1).........	6,565,000	6,611,000	+46,000
Benefits to Former Personnel (13.0)........	200,000	206,000	+6,000
Travel (21.0)..............................	1,108,000	1,119,000	+11,000
Transportation of Things (22.0)............	190,000	197,000	+7,000
Rental Payments to Others (23.2)...........	4,000	5,000	+1,000
Communications, Utilities, and Miscellaneous Charges (23.3)..............	1,645,000	1,641,000	-4,000
Printing and Reproduction (24.0)...........	988,000	1,016,000	+28,000
Consulting Services (25.1).................	831,000	845,000	+14,000
Other Services (25.2)......................	8,599,000	8,265,000	-334,000
Purchases from Government accounts (25.3)..	26,223,000	27,710,000	+1,487,000
Supplies and Materials (26.0)..............	7,530,000	7,610,000	+80,000
TOTAL..................................	85,904,000	88,506,000	+2,602,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Significant Items in House and Senate Appropriations Committee Reports

Item	Action to be Taken
1995 House Report	
Fertility Drugs	
1. The House in its report 103-553, page 55 stated..."The Committee is concerned about the testimony it heard regarding a possible link between certain drugs commonly used in fertility treatment and ovarian cancer, and encourages the Institute to vigorously study whether there is, in fact, such a link putting women at increased risk for ovarian cancer."	1. During the past two years reports have been published describing a possible link between certain drugs commonly used in fertility treatment and ovarian cancer. These drugs are used by many women (including some women who are not infertile themselves but are donating eggs). NICHD has recently funded a large cohort study to determine whether infertile women who have used fertility drugs are at higher risk for cancer and other possible serious side effects than are infertile women who have not used these drugs. The study population will comprise approximately 12,000 women evaluated for infertility in King County, Washington, during the period from 1974 to 1993. The research team, at the Fred Hutchinson Cancer Research Center, will identify those in the cohort who developed ovarian or breast cancer or several other serious adverse conditions, and determine whether any of these outcomes occurred more frequently among women who had used fertility drugs than would be expected. In addition to overall comparisons, separate analyses will be performed for various

Item	Action to be Taken
	subgroups defined by such variables as type of infertility, fertility treatment regimen, and tumor type, among others. It is anticipated that the results of this project will provide important information for evaluating the risks of fertility drug exposure for both infertile women and egg donors. Results from this project are expected within four and a half years.
Demographic Research	
2. The House in its report 103-553, page 55 stated..."The Committee urges NICHD to continue to adequately fund its demographic research programs."	2. Research supported by the NICHD demographic and behavioral sciences program provides information on factors affecting trends in premarital childbearing, teen pregnancy single parent families, immigration, residential segregation, infant mortality and other topics relating to the growth and changing characteristics of our nation's most valuable asset, its population. Research also focusses on the consequences of demographic trends for individuals, familial and societal well-being. Demographic research is a very high priority of the NICHD. In FY 1994, a new demographic and behavioral research center was funded and a new comprehensive study of the factors that create health risks or promote good health for adolescents was launched. NICHD will continue to emphasize funding in demographic and behavioral research and will insure that adequate resources are provided for this important research area.

Item	Action Taken or to be Taken
1994 Senate Report	
Infant Mortality	
1. The Senate in its report 103-318, page 87 stated..."The Committee encourages the Institute to investigate effective interventions to prevent infant mortality in native American communities."	1. A major focus of the NICHD is the development of interventions for preventing or treating low birth weight, preterm births, and for reducing the risks for SIDS which are the top causes of infant mortality. Since infant mortality rates are much higher among Native Americans than the general population, this is a problem of particular concern to this ethnic group. The NICHD supports several infant mortality projects specifically targeted towards Native Americans. One of these studies is investigating infant mortality in the Aberdeen area of the Indian Health Service where the death rate due to SIDS is three times that of the remaining population in North and South Dakota. A significant portion of the Aberdeen project funded by the NICHD includes a systematic analysis of the brains of all infants autopsied in the infant mortality study. The NICHD also supports a neonatal intensive care unit center located at the University of New Mexico which is the designated regional center for the care of high risk pregnant women and critically ill infants in New Mexico. Between 11 and 14 percent of the infants in this ethnically unique center are Native Americans. Another NICHD supported project is developing interventions that promote breastfeeding and reduce infant morbidity rates on the Navajo Indian Reservation.

Item	Action to be Taken
	In addition to these projects specifically targeted towards Native Americans, NICHD supports a broad program of infant mortality research that will ultimately benefit all populations. New initiatives in this area follow. The Perinatal Research Branch located at Georgetown University was initiated in 1992 and is focussing on such problems as premature labor, fetal growth retardation and birth defects in an effort to reduce infant mortality. The cooperative community-based perinatal research program was recently initiated to ascertain the factors associated with the well being of mothers and infants, investigate interventions aimed at improving parenting skills, and to develop and test interventions for reducing unintended pregnancies, preterm delivery and infant mortality, especially among minorities. In addition, in 1994, the NICHD launched a national media campaign with the American Academy of Pediatrics to reduce the risk of Sudden Infant Death Syndrome (SIDS). An evaluation of the campaign effort and impact is underway.
Childhood Research	
2. The Senate in its report 103-318, page 87 stated.."The Committee urges the Institute to continue its commitment to this program by issuing ongoing announcements in the area of middle childhood development."	2. The NICHD is continuing its long term research initiative on development during middle childhood. The NICHD jointly issued a Request for Application with the NIMH. NICHD funded five of the applications and the NIMH funded one. The six grantees will meet in the summer of 1995 to exchange information.

Item	Action to be Taken
	The research to be conducted should reveal social, emotional and cognitive patterns related to normal development in this crucial part of the life span. In addition, some of the new knowledge obtained should provide clues about factors that lead to development of health risk behaviors that have the potential for leading children awry as they enter their adolescent years.
Normative Behavior	
3. The Senate in its report 103-318, page 88 stated.."The Committee encourages NICHD to issue continuing announcements in the area of normative research on ethnic minorities."	3. NICHD believes that the normative development of ethnic minorities and the conditions that influence it are important research areas. This year the NICHD will fund a group of studies that addresses many of the factors that affect child health among Hispanic subpopulations. Among the topics to be studied are infant mortality, chronic disease, migration, assimilation, and inter-cultural differences. This interdisciplinary research will expand our understanding of Hispanic subpopulation characteristics and how they affect child health. In addition, in July of 1994 six new longitudinal studies of ethnic minority families with disabled children were funded. Most of these studies address the development of mentally retarded children and their normally developing siblings and include comparison groups of families without disabled family members. Research questions include cultural beliefs about the nature and cause of disabilities; functions and values of retarded persons in the family and society; support

Item	Action to be Taken
	systems used by different ethnic groups and the impact of economic factors on lifestyles, interactions, access, and receptiveness to various types and forms of services. In addition to these projects, the NICHD also funds research on the development of minority children through its investigator initiated research program and through the support of the NICHD study of Early Child Care.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amt. Authorized	1995 Appropriation	1996 Amt. Authorized	1996 Budget Estimate
Research and Investigation..	Section 301	42§241	Indefinite	$492,033,000	Indefinite	$507,918,000
National Institute of Child Health and Human Development..............	Title IV, Part E	42§285g	Indefinite		Indefinite	
National Research Service Awards....................	Section 487	42§288	such sums as necessary	18,123,000	Such sums as necessary	18,259,000
Total, Budget Authority...				510,156,000		526,177,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Appropriation History

Year	Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$309,119,000 2/	$368,509,000	$362,866,000	$366,780,000
1988	322,032,000	405,673,000 3/	408,334,000	396,811,000
1989	397,945,000 4/	407,650,000 5/	431,388,000	425,649,000 6/
1990	417,064,000 7/	448,493,000	450,593,000	449,087,000 8/
1990 Sequester				-6,173,000
1991	461,473,000	488,282,000 9/	480,645,000	478,956,000 10/
1991 Sequester				-6,000
1992	520,584,000	524,661,000	523,826,000	518,251,000 11/
1993	545,238,000	534,094,000	534,094,000	527,788,000 12/
1994	542,357,000	555,195,000	555,195,000	554,881,000
1995 13/	516,736,000	513,159,000	513,159,000	512,852,000 14/
1996 13/	526,177,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance spread the funding among the Institutes, including $2,186,000 for NICHD.

3/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

4/ The 1989 request excludes funds for AIDS research and education ($20,443,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $14,738,000 in NRSA training programs not considered.

6/ Excludes enacted administrative reduction of $5,739,000.

7/ The 1990 request excludes funds for the National HIV program ($27,129,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

8/ Excludes enacted administrative reduction of $1,506,000.

9/ Excludes $16,562,000 in NRSA training programs not considered.

10/ Excludes enacted administrative reductions of $11,876,000 and $1,913,000.

11/ Excludes enacted administrative reductions of $180,000, $5,048,000 and $973,000.

12/ Excludes enacted administrative reductions of $4,273,000, $29,000 and $2,004,000.

13/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research in FY 1995 and FY 1996.

14/ Excludes enacted administrative reductions of $242,000, $51,000, and $264,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Research for Mothers and Children........	--	$248,380	--	$254,759	--	$251,236	--	$259,932	--	$267,758	--	+$7,826
Population Research...	--	135,368	--	129,364	--	134,592	--	138,226	--	142,767	--	+4,541
Medical Rehabilitation Research............	--	7,270	--	9,995	--	14,195	--	15,007	--	16,000	--	+993
Subtotal.........	--	391,018	--	394,118	--	400,023	--	413,165	--	426,525	--	+67,579
Intramural Research....	370	66,401	363	69,628	316	69,648	320	70,726	315	72,725	(5)	+1,999
Research management and support..........	207	26,429	199	25,214	188	26,003	188	26,265	188	26,927	--	+662
Total obligations..	577	483,848	562	488,960	504	495,674	508	510,156	503	526,177	(5)	+16,021
Unobligated balance lapsing...............	--	174	--	---	--	45	--	---	--	---	--	---
Total, budget authority.	577	484,022	562	488,960	504	495,719	508	510,156	503	526,177	(5)	16,021

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Child Health and Human Development

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
504	$495,719,000	508	$510,156,000	503	$526,177,000	- 5	+$16,021,000

General Statement

This document provides justification for the FY 1996 Non-AIDS activities of the National Institute of Child Health and Human Development. Justification of NIH-wide FY 1996 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute of Child Health and Human Development (NICHD) is that component of the NIH which is responsible for conducting and supporting research on maternal and child health, the population sciences, and medical rehabilitation.

Research encompassed by these areas targets infant mortality; prevention of birth defects, including genetic diseases; learning disabilities; the development and evaluation of contraceptives and infertility treatments; mental retardation and developmental disabilities; developmental and reproductive biology; vaccine development; fetal medicine; demographic and behavioral research; and enhancement or restoration of function in individuals with a physical disability.

Research supported and conducted by the NICHD is multi-disciplinary and ranges from studies using the latest tools of molecular biology to unravel the mysteries of human development, from conception throughout adulthood; to studies of the dynamics of human behavior; to research using bioengineering to develop materials or devices to restore or enhance function in individuals with physical disabilities.

This research is carried out by five administrative entities: the Center for Research for Mothers and Children, the Center for Population Research, the National Center for Medical Rehabilitation Research, the Division of Epidemiology, Statistics and Prevention Research, and the Division of Intramural Research.

The President's appropriation request of $526,177,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Child Health and Human Development during the last five years has been as follows:

	Amount	FTEs
FY 1991	$446,379,000	524
FY 1992	484,022,000	577
FY 1993	488,960,000	562
FY 1994	495,719,000	504
FY 1995	510,156,000	508

Purpose and Method of Operation

The NICHD carries out its extramural programs in research for mothers and children, population, and medical rehabilitation through support of research project grants, center grants, other research grants, training grants and fellowships, and research and development contracts. In addition, the Institute supports an intramural research program that includes prevention research. The scientific and administrative management of the Institute is funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1996 budget request for the NICHD totals $526,177,000. This represents an increase of $16,021,000, or 3.1 percent, over the FY 1995 appropriation. Of the increase requested, $5,786,000 is targeted towards special areas of emphasis to highlight NIH and PHS initiatives for FY 1996. The NIH areas of emphasis and the corresponding targeted increases follow: disorders of developmental and reproductive biology - +$3,350,000, gene therapy - +$500,000; prevention - +$667,000; Clinical Center training - +$92,000, communications infrastructure - +$195,000. The NICHD request also includes a targeted increase of $982,000 for breast cancer research.

The FY 1996 request includes support for 503 full time equivalent positions (FTEs). This is a reduction of 5 FTEs from the FY 1995 appropriation of 508. It is expected that this reduction will be accomplished through attrition.

The NICHD budget request for research project grants is $288,399,000, an increase of $6,845,000 or 2.4 percent over the FY 1995 appropriation. The request will support 884 noncompeting grants at an average cost of $243,705 and 267 competing grants at an average cost of $225,547. This compares to 939 noncompeting and 253 competing awards in FY 1995. Within this mechanism, the following increases are requested for NIH and PHS emphasis areas: disorders of development and reproductive biology - +$2,079,000; prevention - +$667,000; and breast cancer - +$267,000.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1995 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

In research centers, 78 centers in FY 1996 are requested for $48,282,000. This represents the same number of centers and a 3.1 percent funding increase over the FY 1995 appropriation.

Funding for activities in the other research mechanism which includes research career awards, cooperative clinical research, minority biomedical research support and other research grants would be supported for a total of $32,897,000. This reflects approximately the same program level and an overall 2.9 percent increase over the FY 1995 appropriation. Within the cooperative clinical research mechanism, an increase of $670,000 is requested for research on disorders of development and reproductive biology.

The request for R&D contracts is $38,688,000, an increase of $4,006,000 or 11.6 percent over the FY 1995 level. The increase includes funds to maintain the current level of effort in existing programs and funds to support the Institute's Perinatology Research Branch located at Georgetown University in Washington, D.C.. In addition, $715,000 is requested for breast cancer research and $115,000 is requested for research on disorders of developmental and reproductive biology.

In research training, the Institute will support 750 full-time equivalent trainees in FY 1996 for $18,259,000. This is an increase of 2 trainees and $136,000 over the FY 1995 appropriation.

In intramural research and research management and support, FY 1996 funding levels are $72,725,000 and $26,927,000, respectively. In both programs, mandatory cost increases are offset by reductions in administrative costs, FTE employment levels and bonus pay. Within the intramural research mechanism, $1,078,000 is requested for the following NIH emphasis areas: developmental and reproductive biology +$486,000; gene therapy - +$500,000; and Clinical Center Training - +$92,000. Within research management and support, an increase of $195,000 is requested for communications infrastructure which is also a NIH emphasis area.

National Institute of Child Health and Human Development

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
$400,023,000	$413,165,000	$426,525,000	+ $13,360,000

The extramural research programs of the NICHD is comprised of the following budget activities: Research for Mothers and Children, Population Research, and Medical Rehabilitation Research.

Funding for the NICHD extramural research programs during the past five years has been as follows:

	Amount
FY 1991	$363,289,000
FY 1992	391,018,000
FY 1993	394,118,000
FY 1994	400,023,000
FY 1995	413,165,000

Rationale for the Budget Request

The FY 1996 request for the NICHD extramural programs is $426,525,000, an increase of $13,360,000 over the FY 1995 level. These funds will provide support for the following activities: Research for Mothers and Children, $267,758,000, an increase of $7,826,000 or 3.0 percent over the FY 1995 estimate of $259,932,000; Population Research, $142,767,000, an increase of $4,541,000 or 3.3 percent over the FY 1995 estimate of $138,226,000; and Medical Rehabilitation Research, $16,000,000, an increase of $993,000 or 6.6 percent over the FY 1995 estimate of $15,007,000. Examples of current program activities and future plans are described below.

RESEARCH FOR MOTHERS AND CHILDREN

The Center for Research for Mothers and Children (CRMC), one of the three extramural divisions of the National Institute of Child Health and Human Development, is the primary focus of support for research and research training concerning maternal and child health at the National Institutes of Health. Biomedical and behavioral research programs supported by the CRMC range from conception to maturity. These programs are designed to advance the goal of ensuring the birth of healthy babies who have the opportunity to reach adulthood unimpaired by physical or mental disability and, therefore, able to achieve their full genetic potential. The CRMC has a special interest in programs designed to prevent prematurity, low birth weight and Sudden Infant Death Syndrome, conditions which are related to infant deaths in the U.S. Other CRMC research programs have as a goal the prevention or amelioration of birth defects, mental retardation, learning disabilities, pediatric AIDS, childhood injury, and other conditions which impede optimal physical or behavioral development. The CRMC also supports studies of normal physical, cognitive, psychological and social development to understand these processes and identify what may interfere with optimum growth and development. Knowledge acquired from these studies will be used to design more effective intervention strategies.

Infant Morbidity and Mortality: The NICHD Newborn Intensive Care (NICU) Network is conducting a number of studies which will improve the outcome and decrease the cost of care of very low birth weight infants. In a study recently analyzed by the NICU Network, antenatal steroid administration was associated with a 50 to 60 percent reduction in the risk of mortality and morbidity (brain hemorrhage, respiratory distress syndrome, and chronic lung disease in survivors) in very low birth weight (VLBW) infants. An estimated 7,000 additional VLBW infants would survive annually if 60 percent of the mothers of preterm infants received antenatal steroids. It could also result in significant savings--a minimum of 150 million dollars per year in the cost of their initial hospitalization.

NICHD is continuing a large interdisciplinary study of the sequelae of intrauterine drug exposure. Twenty thousand women will be screened to enroll more than 1,000 infants to be followed for 3 years to assess acute and long-term development and the life circumstances of these infants and their families, including service requirements, quality of parenting, ongoing drug exposure, the role of violence, and lead exposure.

Preterm birth is the leading cause of perinatal mortality and morbidity. The strongest risk factor for preterm birth is a previous preterm birth, but biomarkers of risk have been elusive. One marker recently identified is a protein associated with fetal membranes and placenta: fetal fibronectin. The NICHD Maternal Fetal Medicine (MFM) Network recently completed a detailed prospective study of 2,000 women to assess the value of fibronectin and other biomarkers of risk. Patients with a positive test anytime between 24-30 weeks gestation had more than a one in three chance of delivering prematurely (less than 37 weeks gestation). More strikingly, those positive at 24 weeks stood a one in two chance of delivering an extremely premature baby (less than 30 weeks gestation). These strong associations offer significant promise that fibronectin screening in pregnancy, perhaps in combination with other markers, can be used to target resources for research, clinical care, and possibly prevention of preterm birth.

The prevalence and severity of asthma in the U.S. population is increasing. Asthma is one of the most common, and probably the most potentially serious, complication of pregnancy. However, the extent to which asthma contributes to perinatal mortality, prematurity, low birth weight and neonatal hypoxia is uncertain. Also, the effectiveness of asthma managements, including medication, is not well studied in pregnancy. Therefore, the NICHD MFM Network in collaboration with the National Heart, Lung and Blood Institute recently began an observational study of 2700 asthmatic women during pregnancy, using contemporary measures of lung function and management. Also, a randomized clinical trial is planned to compare the effectiveness of a newer anti-inflammatory asthma medication during pregnancy with a traditional medication. These studies will provide better understanding of this clinical problem and provide stronger evidence on which to base effective care.

In June of 1994, under the leadership of NICHD, the U.S. Public Health Service launched a national "Back to Sleep" information campaign in collaboration with the American Academy of Pediatrics, the SIDS Alliance, and the Association of SIDS Program Professionals. This public information campaign is promoting the message that "healthy infants be placed to sleep on their back or side to help reduce the risk of Sudden Infant Death Syndrome (SIDS)." An evaluation of the campaign effort and impact is underway.

Childhood Research: The NICHD jointly issued an RFA in the area of middle childhood with the National Institute of Mental Health (NIMH). NICHD funded five of the applications and the NIMH funded one. The six grantees will meet in the summer of 1995 to exchange information and discuss progress on their research.

NICHD is currently supporting six grants, submitted in response to an RFA, on the topic of normative development of minority children. The NICHD grantees will hold a symposium in April of 1995 to disseminate their research findings to members of the scientific community who study child development.

NICHD supports three Learning Disabilities Centers that focus on discovering the etiology of all types of learning disabilities. A recent discovery on the genetic basis for dyslexia--(reading disorder)--that emanated from the Learning Disabilities Center in Boulder, Colorado, was reported in the October 14, 1994, issue of *Science*. The scientists there studied three generations of families with learning disabilities. They found that the reading difficulties exhibited by the children were associated with anomalies in a gene on chromosome 6. The finding is significant because, if the specific gene is isolated, a test could be developed to identify children, early in life, who are likely to have reading difficulties.

Autism: Autism is a severely incapacitating life-long developmental disability that typically appears during the first three years of life. Some of the behavioral symptoms of autism include disturbances in the rate of appearance of physical, social and language skills, abnormal response to sensation, and abnormal ways of relating to people, objects and events. The result of a neurological disorder that affects functioning of the brain, autism is estimated to occur in approximately fifteen out of every 10,000 births. It is four times more common in boys than girls. Because of the urgency of the problem, NICHD, together with three other Institutes at NIH, will be sponsoring two conferences on autism in 1995 to assess the current state of research in autism, identify unmet needs, and suggest directions for future research.

Rett Syndrome: Rett syndrome is a neurological disorder that occurs only in girls. It has an estimated frequency of 1/15,000 births. Development appears normal up to about six to eighteen months of age. A period of stagnation or regression follows, during which the child loses purposeful use of the hands, followed by further loss of neurologic function, seizures, abnormal curvature of the spine, ultimately leaving the patient totally helpless. NICHD-funded investigators have observed that several girls with Rett syndrome suffer from moderate to severe malnutrition. Several factors may contribute to this problem including poor caloric intake secondary to swallowing difficulties and energy expenditure used to sustain motor activities at the expense of growth. To increase caloric intake, a program of supplemental feeding has been initiated consisting of oral/nasal gastric tube or gastrostomy. This program has resulted in significant gains in weight and height over a short period of time. Additionally, parents frequently note that with improved growth, their daughters show improved alertness and interaction. These preliminary results suggest supplemental feedings can make a difference in growth and well-being in patients with Rett syndrome.

Gene Therapy: The important role of genes in causing disorders of the central nervous system, including many that are associated with mental retardation and developmental disabilities, has become increasingly recognized. The limited number of approaches to treat genetic disorders, such as dietary treatment, enzyme replacement, drug therapy, are usually ineffective and generally require life-long treatment. Because of rapid advances in our understanding of gene function and regulation, research in gene therapy is actively being pursued as another approach for the treatment of mental retardation and developmental disabilities. NICHD recently funded three program projects on gene therapy to investigate several approaches aimed at preventing or ameliorating the harmful consequences of genetic abnormalities.

Bionutrition: The NICHD supported a randomized trial of zinc supplementation in pregnancy in which 3,556 pregnant women were screened for serum zinc levels; the women who had the lowest zinc plasma levels were randomized to receive either daily zinc supplementation or placebo. Results indicated a dramatic effect of zinc supplementation on pregnancy outcome in non-obese women: their babies were heavier and infant head circumference increased as well. This important research provides a simple treatment to decrease the frequency of a significant medical problem and supports the inclusion of zinc in prenatal multivitamin and mineral tablets.

NICHD-supported investigators studying the relationship between sugar intake and hyperactivity found no effect of sugar, aspartame, or saccharine on children's behavior, not even on the behavior of children who were identified as being sensitive to sugar by their parents. This study supplies the scientific evidence to end twenty years of controversy.

Pediatric Pharmacology Research Units: The NICHD has initiated a network of seven Pediatric Pharmacology Research Units (PPRU) in order to provide resources for establishing safe and effective drug dosage regimens for children. These resources are needed because more than three-quarters of the drugs marketed in the United States, including many of the most useful agents in modern therapy, are not approved as safe and effective for use in children. The ultimate goal of the network is to establish appropriate labeling for all drugs prescribed for children.

Child Health Research Centers (CHRC) Program: The CHRC Program was funded to speed the application of advances in basic science to clinical pediatric problems. The mechanism chosen for this effort was support for pilot studies using methods of basic science by young pediatric faculty members. One such investigator has been investigating why the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) acts to excite rather than inhibit the immature nervous system. He was able to demonstrate that bicarbonate is permeable through the GABA channel, and that bicarbonate flux across the cell membrane can explain the paradoxical excitation. This critical difference may preclude the use of anticonvulsants such as phenobarbital and diazepam in infancy.

Birth Defects: Birth defects account for more than 20 percent of infant deaths, making them the leading cause of infant mortality in the United States. Even if they are not lethal, birth defects impact enormously on the physical and emotional health of affected children and their families. Basic research and innovative technology provide new avenues to knowledge needed for meaningful therapy and prevention. Genes that are developmentally important and relevant to human disease are now being identified and characterized through animal models in combination with human studies. Ongoing research is defining how genetic cascades regulate cell proliferation, cell differentiation, cell interactions and cell fate. The roles of environmental agents and nutritional factors are also being investigated. Basic genetic and molecular studies have led to a number of important and exciting findings directed at understanding normal development and the underlying mechanisms associated with birth defects. These include: the identification of genes causing birth defects; development of a new animal model in mice for Sudden Infant Death Syndrome; and the first application of gene therapy to successfully treat two children with severe combined immunodeficiency.

POPULATION RESEARCH

The NICHD's Center for Population Research (CPR) is responsible for the primary Federal effort in population research. CPR supports research and research training in the biomedical, demographic and behavioral sciences. Funding is provided for fundamental biomedical research in the reproductive sciences relevant to problems of human fertility and infertility, the development of safe and effective methods for fertility regulation, the evaluation of the benefits and risks of current contraceptive methods and fertility related technologies and demographic and behavioral sciences research on the causes and consequences of population structure and change.

Demographic and Behavioral Sciences: Research supported by the demographic and behavioral sciences program provides information on factors affecting trends in premarital childbearing, teen pregnancy, single parent families, immigration, residential segregation, infant mortality and other topics relating to the growth and changing characteristics of our nation's most valuable asset, its population.

Immigration has profound implications for the health and well-being of our nation's people. A ground-breaking study of the determinants and consequences of legal and illegal Mexican migration to the U.S. found that recent efforts to control illegal immigration through legislation had not deterred movement across the border, but had resulted in pronounced labor market effects. Future research on immigration and its effects will be enhanced by new data on immigrant status collected by the Current Population Survey.

The NICHD has initiated a program of research on social, behavioral and cultural factors affecting child health outcomes in Hispanic populations. These studies will include research on how two important aspects of health - infant mortality and teen pregnancy - are affected by immigration, assimilation and length of residence in the U.S.

Adolescent health problems cost the taxpayers billions of dollars each year. In 1994, NICHD launched a comprehensive study of the individual, social and environmental factors that create health risks or promote good health for adolescents. The study responded to a directive in the NIH Revitalization Act of 1993. Its unique design will enable researchers to look not only at how characteristics of the individual adolescent - such as attitudes, knowledge and skills - affect health, but also at how health is shaped by the social and physical environments in which adolescents live.

For black youth between the ages of 15 and 24, violence is the leading cause of death. Research supported by NICHD provides the basis for developing and evaluating intervention programs to reduce violence and related behaviors in youth. With funding from the NIH Office for Research on Minority Health, NICHD supports a set of eight cooperative agreements to develop, implement and evaluate coordinated programs of community based health behavior interventions designed to focus on strategies for decreasing violence-related injuries and death, sexually transmitted diseases (STDs) and unwanted or unintended pregnancies in minority youth ages 10-18.

Contraceptive and Reproductive Evaluation: The Institute supports research on the medical effects of contraceptive drugs and devices; on the role of non-contraceptive gynecological products or procedures, such as postmenopausal hormones and fertility drugs; and on the role of barrier contraceptives (including spermicides) in disease prevention as well as contraception.

Several epidemiologic studies have shown a notable decrease in cardiovascular disease among women who take menopausal hormone replacement therapy (HRT). The Postmenopausal Estrogen and Progestin Intervention (PEPI) Trial was a controlled clinical trial of four hormone regimens; it provides the first data to indicate that hormone therapy improves a woman's risk factor profile for cardiovascular disease. None of the regimens affected blood pressure. Although definitive evidence for protection against cardiovascular diseases awaits completion of a large clinical trial, these results provide useful information for women and their physicians making decisions about HRT.

Most intrauterine devices (IUDs) were removed from the U.S. marketplace in the early 1980s, following the Dalkon Shield debacle. A new generation of IUDs is now available and has met with acceptance in many countries outside the U.S. The basic public health issue is that, although the IUD is a highly effective form of contraception, questions remain regarding its safety. Preliminary results of a NICHD-supported randomized double-blind clinical trial indicate that U.S. women can safely use the new copper TCu-380A IUD, and that it is a safe and effective contraceptive.

During the past two years, reports have been published describing a possible link between drugs commonly used in fertility treatment and ovarian cancer. These drugs are used by many women (including some women who are not infertile themselves but are donating eggs). NICHD has recently funded a large study to determine whether such drugs increase the risk of ovarian or breast cancer. Results of this study are expected in about 4 1/2 years.

The FDA recently approved the female condom as a female controlled barrier contraceptive that offers protection against STDs. Since this approval was expedited to provide a needed device to the public, FDA requested NIH to conduct a post-marketing study. NICHD designed and funded a clinical trial to evaluate the protection afforded by the female condom against gonorrhea and chlamydia. In addition to comparing rates of infection among users to that of nonusers, this study will also compare infection rates among women relying on the female condom to those relying on the male condom.

Contraceptive Development: The contraceptive development program supports clinical trials and laboratory studies aimed at developing and improving methods of fertility regulation for both men and women that are safe, effective, reversible and acceptable to various population groups. The program has completed pharmacokinetic and safety studies on both a long-acting injectable progestational agent and an androgen. Clinical studies are expected to start soon in the United States. The progestational steroid is expected to provide contraception for three to six months following a single injection in women while the androgen should provide three months of replacement for a male hormonal type contraceptive regimen.

NICHD investigators have synthesized several new orally active estrogens. In animal studies, these compounds appear to have fewer side effects than those associated with the currently available estrogens, notably alterations in liver function and clotting disorders. Basic endocrine studies, development of radioimmunoassays and pharmacokinetic work have been done.

The Contraceptive Development Branch is currently developing solicitations for a network of clinical sites and a core data analysis center to rapidly assess the potential utility and safety of contraceptive products which emanate from the Branch's programs.

Development of barrier methods that prevent pregnancy and STDs, including HIV, is a critical research area. Preliminary reports from clinical evaluation of new nonlatex (polyurethane) condoms indicate that they have a very low breakage and slippage rate and are preferred over the latex condoms. Better chemical barriers--(spermicides/microbicides)--are urgently needed. In addition to the synthesis and formulation of new compounds, the dosage and longevity of the current products are being clinically assessed to better define the minimum effective dose. Various formulations--(foams, suppositories, films)--are being tested for efficacy and vaginal irritation.

Reproductive Sciences: The reproductive sciences program of the NICHD actively promotes and supports basic and clinical research designed to both expand our knowledge of human reproduction and translate such knowledge into clinical applications for improving reproductive health.

Infertility affects 2.4 million married couples in the U.S., and its health care cost exceeds $1 billion annually. Male factor infertility represents at least 40 percent of the reported infertility cases in the U.S. Little progress has been made with respect to accurately diagnosing, alleviating, or curing male infertility. The NICHD has recently funded four clinical projects focused on male infertility. In addition, a NICHD investigator has developed the first animal model to study spermatogonial stem cell transplantation as a potential method for treating infertility. The method involves transferring germinal cells that populate the testis and generate spermatozoa in a previously barren testis. Such cells repopulate the testis and restore fertility. In addition to infertility treatment, this approach could safeguard fertility of male cancer patients undergoing chemotherapy.

Female factor infertility represents at least 50 percent of the incidence of infertility in the U.S. In certain cases, a normally ovulating female fails to conceive due to what is termed a "hostile" cervix, a circumstance where sperm transport is inadequate. Very little is known about the actual cell biology of the cervix. Recently a young NICHD supported physician-scientist devised an *in vitro* cervical tissue culture system that will allow the laboratory study of human cervical cell functions. This model has great promise for discovering and elucidating the functional differences underlying the "hostile" state of the cervix associated with infertility.

The Infertility Centers program continues to utilize a multidisciplinary approach to coordinate a number of projects studying disorders of ovulation which account for almost half of female infertility. One immediate result from this Center program has been the development of a treatment for a specific type of infertility which is a common unwanted side-effect of surgical or radiation treatments for cranial tumors in women. A procedure has been devised for replacement of the key reproductive hormone (GnRH) suppressed by injury to the secreting brain cells in such patients. Ovulation occurred in 78 percent of the patients treated and all ovulatory patients who desired fertility becoming pregnant.

Uterine fibroids, also known as myomas, are a very common and distressing reproductive disorder. Affected women experience pain, dysfunctional uterine bleeding, and impaired fertility. Fibroids are a major medical indication for hysterectomy. Although it is known that fibroids are estrogen responsive benign tumors, little is known regarding the mechanism(s) of their initiation and growth. A NICHD investigator recently found that the genes that control two specific proteins are overactive in fibroids, and that this activity is most pronounced when estrogen levels are highest. An understanding of how estrogen acts to promote growth may reveal important knowledge leading to an effective new medical therapies that avoid or reduce the need for surgery.

MEDICAL REHABILITATION RESEARCH

Disability has a major impact, exceeding $200 billion annually, on the U.S. economy, and can have devastating effects on the 48.9 million Americans with disabilities, as well as on their families and communities. The mission of the National Center for Medical Rehabilitation Research (NCMRR) is to improve the health, productivity, independence, and quality of life of persons with disabilities. This is accomplished by supporting research on enhancing the functioning of people with disabilities in daily life. A primary goal of the Center is to bring the health-related problems of people with disabilities to the attention of America's best scientists in order to capitalize upon the myriad advances occurring in the biological, behavioral, and engineering sciences. As the organizational focus for medical rehabilitation research at NIH, NCMRR provides funds for research and research training, facilitates the coordination of relevant research within NIH and with other agencies, and disseminates information to scientists, rehabilitation service providers, and to persons with disabilities and their families.

Epidemiology: Major barriers currently exist to accessing available survey data bearing on health issues relevant to the population of persons with disabilities. Existing data sets are not comparable because they use different definitions, measures, and sampling strategies. A project funded by NCMRR will select the best available national surveys and include them in a uniformly formatted data set--archive--that can be accessed by scientists interested in issues related to health and disability.

Access to Nature Trails: For persons with mobility or visual limitations, use of a nature trail depends upon accurate information regarding its accessibility. A project supported by NCMRR has developed procedures to quantitatively evaluate the accessibility of trails. The resulting information will be incorporated into trail guides that can be used by all outdoor enthusiasts. Using the assessment procedures developed in this study, trail managers in various forestry regions will be able to identify new trails that are accessible to people with disabilities.

Improved Wheelchair Seating: Most available wheelchairs have non-adjustable backrests that promote forward rounding of the spine and posterior tilting of the pelvis. This sitting posture is associated with increased levels of fatigue, back and neck pain, and long-term deformities of the spine and pelvis. Supported by NCMRR through the SBIR grant program, an innovative "Back Support Shaping System" provides wheelchair users with an affordable, lightweight, comfortable and easily adjustable backrest which supports an orthopedically correct seating position as the user engages in a variety of activities.

Decubitus Ulcers: Decubitus ulcers are a major source of secondary disability in persons with movement impairments. In persons with spinal cord injury, for example, voluntary motion and sensory appreciation are lost below the level of injury. Functioning of the autonomic nervous system is compromised, altering body homeostasis and circulation. Little is known about the role of the nervous system in wound healing. Research is being supported by NCMRR to characterize the roles of neuropeptides and nerve growth factor in wound healing. The results demonstrate that the nervous system can modulate a wide range of inflammatory and proliferative processes. Substance P, present in sensory endings in the skin, has been shown to be particularly involved in these processes.

Neurorehabilitation: There is a critical need in medical rehabilitation for measures that can predict patients' functional recovery. This is particularly true for stroke rehabilitation where there are not accurate measures for assessing the efficacy of facilitatory or compensatory interventions which are in wide-spread use. Supported by NCMRR, investigators are drawing upon neuroimaging technology to develop a prognostic tool to predict stroke rehabilitation outcomes. Another goal of this research is to provide anatomically-based measures for assessing the extent of recovery following a stroke.

Imaging and Rehabilitation: There is substantial evidence that the central nervous system of young children is marked by plasticity, the ability to make compensatory changes in its functional architecture. For example, children may regain the ability to speak or walk after damage to the speech or motor areas of the brain. Adults are less likely to respond in this way. Supported by NCMRR, imaging technology is being applied to studying the functional reorganization of the brain in young adults who have sustained brain damage at an early age. These experiments are designed to increase our understanding of the spatial, temporal, and functional limits of human brain plasticity. The resulting knowledge can be used by neurosurgeons to plan surgical strategies that maximize patients' functional capabilities.

Research on the Health of Women with Physical Disabilities: With enactment of the Americans with Disabilities Act, issues associated with the quality of life of persons with disabilities have become increasingly prominent. In view of the well established relationship between quality of life and health, effective interventions are needed for promoting the health of persons with disabilities. Few interventions to promote the health of people with disabilities have been validated systematically, and research on health promotion practices that meet the particular needs of women with disabilities has been especially neglected. An initiative is being planned by NCMRR to encourage the development and evaluation of specific interventions that will enhance the fitness and well being of women with physical disabilities. This initiative will also emphasize improvements in the methodology by which these interventions are assessed. The studies supported by this initiative should augment the knowledge needed to enable women with disabilities to achieve optimal health and to avoid occurrence of secondary diseases or injuries.

Research on Pain Management: Chronic pain is a significant secondary problem that is associated with a variety of primary disabling conditions. Several surveys have suggested that approximately one third of people with physical disabilities experience chronic pain. The NCMRR plans to initiate research to improve the prevention and management of chronic pain experienced by people with spinal cord injury, amputation, cerebral palsy, spina bifida, or traumatic brain injury. This initiative will support research that examines the effectiveness of specific treatments that are currently in use. Studies will also be supported that develop and evaluate new or improved treatments to manage different types of chronic pain.

National Institute of Child Health and Human Development

Intramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
316	$69,693,000	320	$70,726,000	315	$72,725,000	-5	+$1,999,000

The NICHD Intramural Research Program is comprised of the Division of Intramural Research and the Division of Epidemiology, Statistics and Prevention Research. The Division of Intramural Research conducts laboratory and clinical research on reproduction and on the biomedical and behavioral aspects of human development. The Division of Epidemiology, Statistics and Prevention Research conducts field studies of determinants of infant mortality and morbidity and interventions to promote health and well being in mothers and children.

Funding for intramural research during the past five years has been as follows:

	Amount	FTEs
FY 1991	$59,861,000	334
FY 1992	66,401,000	370
FY 1993	69,628,000	363
FY 1994	69,693,000	316
FY 1995	70,726,000	320

Rationale for the Budget Request

The FY 1996 request for intramural research is $72,725,000, an increase of $1,999,000 over the FY 1995 appropriation of $70,726,000. The following are examples of current activities, and future plans.

LABORATORY AND CLINICAL RESEARCH

Scientists in the Division of Intramural Research will continue to pursue promising leads that are broadly concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. The key to the prevention of common "adult" diseases, such as cancer, heart disease, mental illness, immunologic disorders, and premature aging, lies in our understanding of the rules which govern early development. Research is carried out in patients as well as in a diversity of animal models. Currently, two themes of basic investigation are being emphasized throughout the program: The structure, function, and transmission of genes -- knowledge in this area is critical as we embark upon an era of "gene therapy"-- and "signal transduction", the complex pathway by which environmental stimuli induce a signal at the cell surface which eventuates in the expression of genes in the nucleus. There is also an intensive effort in vaccine development, particularly with respect to common but serious bacterial infections of children, and a major emphasis on the development of new methods and tools of interest to biotechnology.

Perinatology Research Branch: The intramural Perinatology Research Branch was established in 1992 to conduct research on pregnancy and perinatology that addresses the most important causes of premature delivery and infant mortality. A permanent site for the clinical and laboratory research of the Branch has been established at Georgetown University in collaboration with Howard University and D.C. General Hospital, and a support contract has been awarded to begin to provide facilities for this Branch. The new Branch is now operational and is pursuing research studies on the role of subclinical infection and cytokines in premature birth. The Perinatal Research Branch published a landmark study last year, describing the first successful endoscoptic surgery on a human fetus. In a case of twin reverse arterial perfusion syndrome, the umbilical cord of an acardiac twin was surgically interrupted using transabdominal thin-gauge fetoscopy, thus saving the life of the normal twin.

Genes controlling early body patterning in the embryo - As a step toward answering how a single fertilized egg cell develops into a complex organism, NICHD investigators have determined that gsk3, the gene that encodes the mammalian enzyme, glycogen synthase kinase-3, plays a role in the formation of the vertebrate body plan. Regulation of this gene, along with a homologous gene in the fruit fly (zw3), is necessary for the proper formation of front-back body orientation. This conservation of a critical embryogenesis gene across such a huge evolutionary distance is reflected in the very similar appearance and development of normal early embryos from very distant phyla. It is likely that zw3/gsk3 will also be shown to play a role in human development.

Gene-altered mouse helps probe Parkinson's disease and drug addiction - A brain deficiency in the neurotransmitter, dopamine, is the basis for Parkinson's disease. To better understand the relationship between dopamine and Parkinson's disease, NICHD scientists have recently developed a transgenic mouse that is missing the gene that encodes for the dopamine D_1 receptor. The D_1 "knock-out" mouse was developed to identify the relative importance and interplay of D_1 and D_2 dopamine receptors. This information will help sort out the complex mechanisms of movement control, which are disrupted in Parkinson's disease. The D_1 mice also should be very useful in probing mechanisms by which cocaine and amphetamine become addictive, since the D_1 receptor mediates the brain's "rewards and learning" pathways.

Over-active immune cells are inhibited by "chemicals-decoys" that block their signalling pathways - The T lymphocytes, or T cells, are a crucial component of the immune system, acting as sentinels to detect and destroy foreign intruders. However, excessive T cell function can also be harmful: some autoimmune diseases, such as rheumatoid arthritis or lupus erythematosus, are thought to be caused by over-active T cells that destroy the bodies own tissues. In an effort to reduce or prevent such diseases, NICHD has been studying the regulation of T cell function. Tyrosine-based activation motifs (TAMS) are cellular mechanisms involved in initiating T cell function after antigen binding. Using a "knock-out" transgenic mouse, researchers found that TAMS are not only important in the immune response, but also for developing the normal diversity of T cells, which is required to respond to a wide variety of antigens. Recently, a chemical decoy ("phospho-TAM") has been synthesized that binds and inactivates the last enzyme involved in mobilizing T cells, thereby blocking the progression of the immune response signal. If these decoy phospho-TAMS can be made to penetrate the cell easily, they might be used to prevent over-zealous T cells from destroying the body's own tissues.

New pertussis vaccine is highly effective and very safe - Clinical trials of a new, single component (detoxified pertussis toxin) vaccine against pertussis (whooping cough), conducted in the midst of a severe whooping cough epidemic in Sweden, have shown that the NICHD-developed vaccine protects 71% of the children receiving it. Besides being highly effective, the new vaccine produces far fewer side-effects than the older whole-cell vaccine.

EPIDEMIOLOGY, STATISTICS AND PREVENTION RESEARCH

The major areas of research in the Division of Epidemiology, Statistics and Prevention Research include the study of congenital malformations, a major clinical trial to evaluate the efficacy of calcium supplementation during pregnancy to reduce the risk of preeclampsia of pregnancy, interventions to directly and indirectly reduce the high infant mortality rate in Washington, D.C., and research on infectious diseases which affect the health of mothers and children, especially E-cholera infections in the newborn as well as group B streptococcal disease around the time of birth. In addition, a population based intervention aimed at preventing problem behavior in children of middle school age is being implemented.

Calcium for Preeclampsia Prevention (CPEP): Preeclampsia, a disease manifested by hypertension and kidney damage, occurs in about 5 to 10 percent of all pregnancies. This disease is responsible for one-fifth of all U.S. maternal deaths and is associated with an increased risk of perinatal mortality.

A major clinical trial to determine if giving pregnant women calcium supplements will reduce their risk of preeclampsia was initiated in June 1991. It will reach its enrollment goal of 4500 women by Marchof 1995 and the results of the analysis of the data from this trial are expected during 1996.

The District of Columbia Infant Mortality Initiative: The NICHD Infant Mortality Initiative in Washington, D.C. is currently implementing an intervention to improve parenting skills in high risk mothers. The program is designed to increase utilization by high risk mothers of preventive health services for their infants and to increase their level of development. Other projects in place or about to be started deal with the assessment of determinants of lack of immunization coverage, of injuries during infancy and the impact of components of neonatal intensive care upon neonatal mortality.

Vitamins to Prevent Spina Bifida and Related Birth Defects: It has recently been reported that folic acid supplementation around the time of conception can reduce the risk of neural tube defects (NTDs). Scientists from

NICHD, Trinity College, Dublin and The Health Research Board of Ireland have shown that there is a metabolic defect related to folate in pregnancies producing offspring with NTDs. Women with affected offspring had significantly higher levels of homocysteine in their blood than women with normal offspring. Thus, an inability to eliminate homocysteine may be critical in the production of NTDs. Folic acid is known to reduce homocysteine, thereby explaining its effectiveness in preventing NTDs. If these findings are confirmed, they will have important public health implications. These investigations are continuing.

Group B Streptococcal Infections: Group B streptococcal (GBS) infections are a major cause of neonatal morbidity and mortality in the United States. Intensive efforts are under way to develop vaccines that can protect newborns by raising maternal anti-serotype serum antibodies and passing across the placenta during gestation. However, little information is available about levels of these antibodies that are associated with protection and that can serve as targets in evaluating new candidate GBS vaccines. NICHD investigators are collaborating with the Food and Drug Administration in planning a study of the relationship between maternal serum anti-GBS antibodies at term and the risk of early-onset GBS disease. It is anticipated that study of the protective role of natural immunity, using well-standardized assays, will set benchmarks for evaluating future GBS vaccines.

Preventing Problem Behavior Among Middle School Students: Problem behavior, including substance use, misconduct, violence and delinquency, increases dramatically during early adolescence, reaching its peak during high school. While a small percentage of adolescents are responsible for a disproportionate amount of problem behaving, precocious experimentation is wide-spread and considered by many to be normative. Youth who develop a positive affiliation with the school develop positive peer relationships and realistic expectations about the outcomes of their actions, and those whose parents monitor their behavior and actively participate in their lives, are protected against precocious problem behavior.

The NICHD is conducting a study to test the efficacy of a multi-component program of school-based interventions in the primary prevention of problem behavior and promotion of prosocial behavior in a sample of middle school students. The study is being conducted in one school district with approximately 4200 multi-ethnic students in seven middle schools. Interventions are being directed toward (1) students to improve their social skills and comportment; (2) the school environment to increase student participation and bonding; and (3) parents to foster student prosocial behavior. The study began in June, 1994 and will be fully implemented by the fall of 1996.

National Institute of Child Health and Human Development

Research Management and Support

Authorizing Legislation - Sections 301, Title IV, Subpart 7
1996 Authorization: Indefinite.

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
188	$26,003,000	188	$26,265,000	188	$26,927,000	--	+ $662,000

The Research Management and Support (RMS) activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: the Office of the Director, the Office of Administrative Management, the Office of Research Reporting, the Office of Science Policy and Analysis, and the Office of Grants and Contracts. Scientific direction and administrative management of the Institute's extramural program is provided by the Institute's Scientific Review Program as well as program staff of the Institute's extramural activities.

Funding for the RMS program during the past five years has been as follows:

	Amount	FTEs
FY 1991	23,229,000	190
FY 1992	26,603,000	207
FY 1993	25,214,000	199
FY 1994	26,003,000	188
FY 1995	26,265,000	188

Rationale for the Budget Request

The FY 1996 request for RMS is $26,927,000, an increase $662,000 over the FY 1995 estimate of $26,265,000. During FY 1996, RMS activity will continue to provide for the professional leadership and technical guidance needed to plan, direct, and implement all programs of the Institute; and to conduct a broad program of information dissemination.

Some specific functions performed by the various components of this activity follow. The Scientific Review Program provides policy direction and coordination of review activities within NICHD involving extramural grant and contract awards. Additionally, this group serves as liaison for applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations. The scientific program staffs of the Center for Research for Mothers and Children, the Center for Population Research, and the National Center for Medical Rehabilitation Research concentrate their efforts on the scientific management of the Institute's grants and contracts and assist in the planning and development of new programs that will best accomplish the mission of the NICHD.

NATIONAL INSTITUTES OF HEALTH

National Institue of Child Health and Human Development

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Ofice of the Director......................	7	7	7
Office of the Deputy Director..............	2	2	2
Office of Administrative Management, Office of Research Reporting, Office of Science Policy and Analysis, and Office of Grants and Contracts............................	87	89	87
Center for Population Research.............	29	30	29
Center for Research for Mothers and Children............................	37	38	37
National Center for Medical Rehabilitation Research..................	9	9	9
Division of Scientific Review..............	17	17	17
Division of Epidemiology, Statistics, and Prevention Research..................	30	31	30
Division of Intramural Research............	286	285	285
Total, NICHD..........................	504	508	503

Average GS/GM Grade

1991......................	9.8
1992......................	10.0
1993......................	10.4
1994......................	11.0
1995......................	11.0
1996......................	11.0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDs Research.

NATIONAL INSTITUTES OF HEALTH

National Institue of Child Health and Human Development

Detail of End-of-Year Employment

	1994 Actual	1995 Estimate	1996 Estimate
ES-6	1	1	1
ES-5	2	2	2
ES-4	9	9	9
ES-1	1	1	1
Subtotal	13	13	13
Total - ES Salary	$1,381,640	$1,385,800	$1,430,000
GS/GM-15	41	41	39
GS/GM-14	46	46	44
GS/GM-13	35	35	34
GS-12	39	39	38
GS-11	32	32	31
GS-10	3	3	3
GS-9	24	24	24
GS-8	35	35	35
GS-7	37	37	38
GS-6	15	15	15
GS-5	10	10	10
GS-4	12	12	12
GS-3	5	5	5
GS-2	3	3	3
Subtotal	337	337	331
Grades established by Act of July 1, 1944 (42 U.S.C.207):			
Assistant Surgeon General	3	3	3
Director Grade	13	13	13
Senior Grade	11	11	11
Full Grade	9	9	9
Senior Assistant Grade	2	2	2
Subtotal	38	38	38
Ungraded	6	6	6
Total permanent positions	394	394	388

Total positions, end of year....	503	503	497
Total full-time equivalent (FTE) employment, end of year.........	504	508	503
Average ES level................	4.0	4.0	4.0
Average ES salary...............	$106,280	$106,600	$110,000
Average GS/GM grade.............	11.0	11.0	11.0
Average GS/GM salary............	$46,300	$47,800	$49,400

THURSDAY, MARCH 30, 1995.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

WITNESSES

DR. PHILLIP E. GORDEN, DIRECTOR

DR. RICHARD EASTMAN, DIRECTOR, DIVISION OF DIABETES, ENDOCRINOLOGY AND METABOLISM

L. EARL LAURENCE, EXECUTIVE OFFICER

CHARLES R. ZELLERS, FINANCIAL MANAGEMENT OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. PORTER. Next and finally, we have the National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK. We're pleased to welcome Dr. Phillip Gorden, the Director. Dr. Gorden, why don't you introduce the people at the table and proceed.

INTRODUCTION OF WITNESSES

Dr. GORDEN. Thank you very much, Mr. Chairman.

On my far left is Mr. Charlie Zellers, our Budget Officer. To my left is Mr. Earl Laurence, our Acting Deputy Director and Executive Officer. To my right is Dr. Richard Eastman, the Director of our Division of Diabetes, Endocrinology and Metabolism. I know you know the gentlemen out to the right.

OPENING STATEMENT

I'll just proceed with my statement. Mr. Chairman, I'm pleased to highlight the research progress and plans of the NIDDK in combatting many of the Nation's most serious, chronic, costly health problems, including diabetes, metabolic diseases, digestive diseases, kidney and blood disorders, and urologic diseases. Understanding these areas is a important issue for our Institute. It includes basic research in the nutritional sciences, endocrinology, molecular genetics and other scientific disciplines.

The striking results of the Diabetes Control and Complications Trial, known as the DCCT, in demonstrating that the eye, kidney and nerve complications of diabetes can be prevented or delayed have given rise to the Diabetes Prevention and Treatment Initiative. This initiative includes both a basic and clinical research agenda and also formulates a new treatment approach to diabetes.

Research in obesity has clearly moved forward with the discovery of an obesity gene in mice that provides information about the regulation of body weight in man. In addition, careful clinical studies have given us new information regarding weight loss and weight gain mechanisms. These studies represent a true milestone in nutrition research.

The discovery of the abnormal gene that results in adult polycystic kidney disease has provided a new focus for research into the cause of this most common genetic disease of the kidney. Further, clinical research demonstrating that both drugs and blood pressure manipulation can protect the diseased kidney has given rise to studies designed to impact the enormous cost of end-stage renal disease.

Prostate growth can now be controlled with drugs developed through research. This forms the basis of a new approach to both understand and treat benign prostatic hyperplasia. In addition, we've put into place a clinical database and a series of basic studies to understand interstitial cystitis and other bladder diseases of women.

The fundamental studies that demonstrated a bacterial cause of duodenal ulcers have provided an excellent example of how a chronic disease can be treated in a cost effective manner by elimination of a causative agent, H. pylori. Moreover, we have both new insights and progress in our attempt to understand and treat the complex diseases of the digestive tract, such as Crohn's and ulcerative colitis. The discovery of the important red blood cell growth factor, erythropoietin, has provided a major treatment for anemia and a huge focus for the development of the biotechnology industry.

In just the same way, we are now developing a counterpart platelet growth factor, which will have an enormous influence on the treatment of blood clotting disorders and will further stimulate the biotechnology industry. A parallel clinical discovery in our intramural program is the demonstration of the efficacy of hydroxyurea in the treatment of sickle cell anemia.

Finally, we take great pride in the awarding of the 1994 Nobel Prize in medicine to Dr. Martin Rodbell, who, while working in our intramural program, discovered a fundamental mechanism of cell communication. This discovery has major implications for diseases as diverse as diabetes, cardiovascular disease and cancer.

And parenthetically, Mr. Chairman, I might add that about the time this work was being done, a little over 25 years ago, a young clinical associate came to our Institute to begin his biomedical research career. His name was Harold Varmus, and I think the very rich atmosphere of our intramural program is reflected in his very distinguished career.

I hope these few examples convey the vigor and the diversity of the NIDDK research programs. As I noted earlier, many of the diseases within the NIDDK research mission are chronic diseases. Our success in combatting them must often be measured in strides towards more effective therapies, such as that reported for cystic fibrosis in the Washington Post this morning, rather than a single achievement that results in a cure.

Mr. Chairman, the President's budget request for the NIDDK is $748,798,000. I'd be pleased to answer any questions that you may have.

[The prepared statement and biography of Dr. Phillip Gorden follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Diabetes and Digestive and Kidney Diseases

I am pleased to highlight the research progress and plans of the NIDDK in combating many of the Nation's most serious, chronic and costly health problems, including: diabetes and metabolic diseases; digestive diseases; kidney and blood disorders; and urologic diseases. Underlying these areas is a solid foundation of basic research in the nutrition sciences, endocrinology, molecular genetics, immunology, virology and other scientific disciplines.

NIDDK basic research continues to be the wellspring of major achievements in science and medicine. This past year, for example, we were enormously pleased and proud that one of our former intramural scientists, Dr. Martin Rodbell, was a co-recipient of the 1994 Nobel Prize in Physiology or Medicine for landmark discoveries he made while at NIDDK over 25 years ago. In our laboratories, he found that signals are transmitted from outside to inside the cell through the binding of an essential cellular molecule called GTP to what are today known as "G proteins." This work on the mechanisms of cell signaling has broad application to disease processes from diabetes to cancer and to the action of multiple hormones and drugs. Today, NIDDK scientists are continuing to unravel the secrets of cell-to-cell communication in health and disease.

Likewise, the NIDDK will continue its leadership role in structural biology, a cutting edge of modern biomedical research. Structural biology enables us to visualize the actual three-dimensional shape of a molecule by using highly sophisticated imaging techniques. Once the shape of a molecule is known, we can better understand and modulate its function. We essentially have a blueprint for the design and construction of drugs and other agents that can act to modify the biologic molecule whose structure has been disclosed. For example, we are moving rapidly to capitalize on one of the most impressive new advances in AIDS research. NIDDK intramural scientists have discovered the molecular blueprint of an enzyme, called integrase, which the AIDS virus needs to reproduce. In another example, NIDDK intramural scientists have helped to define the shape of a protein encoded by a tumor suppressor gene, called p53, which has both causal and therapeutic implications for several forms of cancer. These types of discoveries will help drive U.S. biotechnology firms toward the commercialization of new drug therapies to benefit patients afflicted by disease and to maintain U.S. pre-eminence in the drug-development arena.

Out of molecular approaches to drug development has emerged the discovery and production of thrombopoietin -- a powerful growth factor for blood platelets. We expect this discovery will have an enormous impact on the biotechnology industry. Its importance is like that of the discovery and genetic engineering of erythropoietin -- a growth factor for red blood cells that is now widely used to combat anemia in kidney failure and other diseases. Similarly, NIDDK intramural scientists laid the basic research foundation for recent, highly successful clinical studies of the drug hydroxyurea for the treatment of sickle cell disease in African Americans. Yet another promising avenue in molecular hematology is research to isolate and characterize stem cells. These are the most fundamental type of cells from which other highly specialized cells later differentiate. They are the key to blood cell regeneration and to the whole concept of gene therapy.

In diabetes, we are pursuing several lines of promising research as part of our Prevention and Treatment Initiative. This multifaceted effort ranges from basic research to find the genes underlying diabetes all the way to major, multicenter clinical trials. We are beginning such trials to prevent the onset of both insulin-dependent diabetes, which most often strikes children and young adults, and of non-insulin dependent diabetes, which disproportionately affects our minority populations. At the same time, we are actively engaged in research to prevent or arrest the eye, nerve, kidney, heart and other devastating disease complications associated with elevated concentrations of blood sugar. Complementing this biomedical research, we are launching a new National Diabetes Outreach Program (NDOP), which will widely communicate the results of a recently completed and highly successful clinical trial, the Diabetes Control and Complications Trial (DCCT). This study showed that maintaining blood glucose levels as close to normal as possible throughout the day can prevent or reduce some of the most serious complications of insulin-dependent diabetes. Lowering blood sugar reduced the risk of eye disease by 76 percent, the risk of nerve disease by 60 percent, the risk of kidney disease by 50 percent, and high cholesterol levels by 35 percent. While the best results were achieved with the tightest control of blood glucose levels, the study showed that any improvement in control had a beneficial effect. To get these results to the public, the NIDDK has developed an information package and pre-recorded 1-800 telephone service based on the message, "Do Your Level Best."

Obesity research is a vital part of our agenda that is spurred by recent seminal discoveries. The impressive identification of an obesity gene in an experimental animal is paving the way to the development of new knowledge about a satiety control system in humans. The obesity gene appears to regulate production of a protein that signals the brain about satiety and fat storage, and thus may be a key to controlling body weight. Our next steps are to isolate the protein encoded by this gene, and then to find ways to correct defects in its function. Although much more research is needed before discovery of the obesity gene will impact on the prevention and treatment of human obesity, we believe that, in locating this gene, we have found a critical piece to the obesity puzzle. In parallel to our basic and clinical research on obesity, we are beginning a new NIDDK outreach program -- the Weight-Control Information Network (WIN). Part of this program is to develop communication strategies for providing the public with science-based information about the prevention and treatment of obesity.

Kidney disease research is being propelled by the finding of the gene responsible for the major form of polycystic kidney disease. This advance has given new impetus to research aimed at understanding this important genetic form of kidney disease, which is the fourth leading cause of end stage renal disease. We hope that kidney research will parallel the extraordinary advances and momentum we have seen in the field of cystic fibrosis. There, the discovery of the CF gene by NIDDK grantees in 1989 fueled the rapid exploration of possible drug therapies and gene therapy research. Also furthering kidney research are two new clinical trials: the "African American Study of Kidney Disease" and "Mortality and Morbidity in Hemodialysis Patients." These multicenter studies are part of our continuing efforts to halt or slow the progression of kidney diseases to irreversible kidney failure. They are building upon the results of our previous clinical trial on the "Modification of Diet in Renal Disease" and on several clinical studies of a group of highly promising drugs called ACE inhibitors.

Urologic diseases are central to the Institute's research portfolio. We continue to work closely with the National Cancer Institute on our common concerns about malignant and non-malignant prostate growth. I am also very pleased to announce that the NIDDK is inaugurating a full-scale clinical trial to assess the role of newly discovered drugs in the treatment of benign prostate enlargement, commonly called BPH. Women's urologic diseases also remain a major focus of NIDDK research, including interstitial cystitis, incontinence, and urinary tract infections. We are actively pursuing research in these areas.

In digestive diseases, the prevention of liver failure is a major objective. We are therefore very encouraged that the death rate due to cirrhosis--a surrogate measure for liver failure--fell 26 percent between 1979 and 1989. We believe that several important research advances have contributed to improved medical management of liver diseases and thus to this downward trend in mortality rates. NIDDK-funded researchers also are uncovering clues about destructive immunologic and inflammatory mechanisms in digestive diseases, such as inflammatory bowel disease. We are committed to sustaining and intensifying this research area.

I hope these few examples convey the vigor and diversity of the NIDDK research programs. As I noted earlier, many of the diseases within the NIDDK research mission are chronic. Our success in combating them must often be measured in strides toward more effective therapies, rather than in a single achievement that results in a cure. A final example I would like to leave with you today is the confirmation, by our recent Consensus Development Conference, of a major advance, from both a medical and economic perspective. In the treatment of duodenal ulcers, there is consensus that this disease is caused by a bacterium called H. pylori and that standard medical practice is to eradicate the bacterium using a simple, inexpensive antibiotic therapy. This new therapy can clearly prevent recurrence of duodenal ulcers--thereby striking at the chronicity of this disease. An NIDDK analysis estimates that this therapy could save hundreds of millions of dollars annually in health care costs. We now hope to explore the Consensus Development Conference's recommendations for additional research, such as studies to explore a possible link between H. pylori and stomach cancer.

Mr. Chairman, the President's Budget Request for the NIDDK is $748,798,000. I would be pleased to answer any questions you may have.

Phillip Gorden, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

December 22, 1934. Baldwyn, Mississippi. Married, two children.

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CYSTIC FIBROSIS THERAPY

Mr. PORTER. Dr. Gorden, thank you for your oral statement. You anticipated my first question with your last remark, the Washington Post article today reporting the study, published in the New England Journal of Medicine, on the use of ibuprofen and its ability to fight the progression of cystic fibrosis.

This finding supports the arguments of those who believe that advances in biomedical research don't always increase health care costs. Unlike many reported findings, can this breakthrough be quickly translated into clinical practice?

Dr. GORDEN. Yes, I think it can. I think the important thing is that individuals with this disease will have to consult their individual physicians to be certain that this treatment is appropriate for them individually. But we believe that this is something that can be instituted immediately with drugs that are available and are cheap.

And I might add, Mr. Chairman, that in addition to this, there are at least two other therapies that have proved effective in the treatment of this disease. One is a simple mechanical device that we believe may take the place of the very intensive pulmonary physical therapy that is frequently required at some stage of this disease, and is very time-consuming for individuals and their families. This device is also very inexpensive, and we believe perhaps will actually be able to replace this very intense physical therapy. In addition, there is an enzymatic treatment that's been developed in the last two or three years that is being produced by biotechnology, and is also an effective treatment.

Of course, all of this is basically what we would believe is a holding pattern for what we hope will be a much larger effort towards gene therapy, now that the defective gene is recognized. We have underway a very intense effort aimed at a direct approach to treatment of cystic fibrosis.

PROGRAM BALANCE

Mr. PORTER. I know you face funding pressures from many disease groups who make up your patient constituencies. But we hear concerns from those involved in diabetes that your Institute has been decreasing over time the share of research funding diabetes receives. Given the health care costs associated with the disease, do you feel you've achieved a reasonable balance among diseases in your research portfolio?

Dr. GORDEN. Our Institute is based on sort of a fundamental mission of diabetes, digestive and kidney diseases. And there's a base of research in each of those areas. Those are the three large areas. We also have a number of smaller areas that are very important: nutrition, urology, hematology and so forth.

Since I've been Director, since 1987, in constant dollars, our Institute budget has only grown by 1.4 percent. And so it's been very important to try and maintain some balance. Because of Congressional directives and other opportunities, certain small programs have grown to some extent. It has been very difficult to make those programs that had a very large base, in a relative sense, grow as much.

And so they've remained more constant, and there's a great deal of concern. Everyone would like to see each of our programs grow. But in fact, what one sees grow are those that have a very small base, with much more of a constancy to those programs that have a larger base. I think it's very important that we maintain some kind of base in all these programs, and we will do the best we can to deal with the stresses in each of our respective communities.

DIABETES AND IMMUNOLOGY

Mr. PORTER. Thank you. I understand that research now suggests that the common coxsackie virus may trigger Type-I diabetes. Can you explain for us how a virus might be involved in diabetes, and if that implies a vaccine might someday be available to prevent the disease?

Dr. GORDEN. There was a period of time when there was a great deal of interest in an acute viral illness, such as we see with influenza, which is an acute viral illness that causes a respiratory problem. There have been occasional cases of diabetes produced by an acute illness, and mumps is a virus that can produce an acute form of diabetes. But these are relatively uncommon.

What you refer to is a new concept called immunologic mimicry, which is that an individual may be exposed to a virus that has a particular protein configuration that the immune system may confuse, for a variety of reasons, with a normal body tissue. If that body tissue happens to be an insulin producing cell, the immune system then may, in an aberrant way, attack that cell.

And so coxsackie virus has been one of the viruses in which there are proteins that suggest this kind of immunologic memory or mimicry. This is a very active area of research, and it has come from several different directions that I could go into. But fundamentally, it relates to this general concept, and is a very active area of research at the present time.

INTERSTITIAL CYSTITIS

Mr. PORTER. Earlier this year, Dr. Gorden, we heard testimony from a young professional woman golfer, Terry Jo Myers, who spoke very eloquently about the hardship and discomfort of living with interstitial cystitis. Congressional interest in this disease has spurred more research in the past few years. Can you tell us if there have been any new findings in the treatment area that will allow people like Terry Jo Myers to lead more normal lives?

Dr. GORDEN. This is an area for which research really is in a very formative period. It is just beginning. Interstitial cystitis refers to a group of painful conditions of the bladder. We don't really know a cause of any of these, and it's better to think of them as a set of conditions involved in producing severe pain, predominantly in women.

We set out to create an underpinning to study this by some very basic mechanisms, some very fundamental mechanisms, and have actually built that program, through one of the largest proportional growth rates of programs in the Institute, up to approximately $9 million in fiscal year 1995, from a base four or five years ago of virtually nothing. It is an area that has considerably expanded.

The other thing we've done is to create a clinical database and begin to enter patients with a common set of symptoms, so that we can begin to understand the clinical manifestations of this disease. Hopefully we will then formulate, through those patients with a defined set of clinical abnormalities, a more clear-cut research focus.

So we're trying to approach this from several different directions. At this point, we have not been able to define a specific cause or specific cure. But there are several things that have been done to make the lives of patients more comfortable, and certainly one of the things that's been done to make them more comfortable is the recognition of the difficulty that these patients are having.

And we, I think, have come a long way in working with the professional societies and working with individuals who are interested in this condition to let them know that we clearly are interested and that we're trying. I think that this has had a very significant effect on individuals like the young woman who testified.

Mr. PORTER. Thank you, Dr. Gorden.

Mr. Hoyer.

Mr. HOYER. Thank you very much.

DIABETES—ECONOMIC COST

Doctor, I don't think you—I was looking here briefly—do you have any figures for the cost of diabetes in this Nation?

Dr. GORDEN. There are several sets of figures, Mr. Hoyer. One set of figures was presented by a study conducted by the American Diabetes Association within the last couple of years. Those numbers range approximately around $91 billion. It depends to some extent on exactly what's included. There are other figures that range higher. I could give you a range of figures that go anywhere from approximately $91 billion which is actually a rather careful estimate of both the direct and indirect costs of the disease, to figures that range higher, depending on the various assumptions that go into collection of these kinds of data, that would range up to a ball park of $130 billion. It is a very large number either way you look at it.

Mr. HOYER. And of your $700 million plus, what portion of that do you ascribe to diabetes?

Dr. GORDEN. Approximately $200 million, or just under. In fiscal year 1995, we estimate approximately $200 million.

Mr. HOYER. What progress have we made vis-a-vis the costs that would have been incurred, and you may not have this figure either. But one of the things that, for instance, the Dental Institute, they were pleased to come in and say, over 20 years you've spent X millions of dollars. The Dental Institute is a smaller Institute, and in fact we have saved 10, 20, 30 times that amount as a result of the efforts of the Institute. Have we made enough progress as a result of work at the Institute and related intramural and extramural for you to make a similar estimate?

Dr. GORDEN. I can't certainly give you a fluoridation answer, Mr. Hoyer. I wish I could. [Laughter.]

Dr. GORDEN. I wish we had a fluoridation preventive for diabetes, but unfortunately we don't. Dr. Eastman has spent a great deal of time estimating what the ultimate cost savings will be, using the data from the Diabetes Control and Complications Trial, because after all, it's the complications of diabetes that incur most of the costs. Yes, there is a considerable cost involved in the treatment of diabetes.

The major part of that cost has to do with the major morbidities of the eye and the kidney and of the vascular system. Using the data that we have, Dr. Eastman certainly has some really excellent projections that we'd be happy to provide for you in a preliminary paper that he has prepared, to give you some idea of what those might be and what the assumptions are that go into this.

We believe, since the results of that trial are so dramatic in reducing the eye and the kidney and the nerve complications of the disease, and those are the things that drive the costs, that if we extrapolate the savings out over the next 10 to 20 years, we will not give you a fluoridation answer, but certainly we will give you a very positive response to decreasing the costs of diabetes.

Mr. HOYER. I'd be interested in getting that. We don't necessarily have to put it in the record, but I'd be interested in seeing it.

Dr. GORDEN. Yes, sir.

DIABETES—PROGRESS IN TREATMENT

Mr. HOYER. The Chairman mentioned the article in this morning's Post in his question to you, about transplant, gene therapy and others. Where do you think we are for diabetes? I mean, what are our expectations? The public that talks to us in town meetings says we spend a lot of money and what's happening. And of course, it's an imprecise answer, at best, I understand.

But there have been some positive signs in recent years with reference to diabetes. Where do you think we are in terms of getting to the point where we get the—I'm not even sure how to characterize what would be perceived by you, for instance, or obviously for those with diabetes, as progress. Curing the diabetes would be fair.

But my question I guess is imprecise, but where are we in terms of overcoming the most debilitating aspects of this disease, and in fact to where we can intervene so that daily insulin and other treatments are not necessary?

Dr. GORDEN. The Diabetes Control and Complications Trial truly placed diabetes and hyperglycemia in the same context as earlier studies have for the treatment of hypertension or hypercholesterolemia. It is very clear now that the morbidity, that is, the complications of the eye and the kidney and the nerve, those that we more commonly talk about, are a result of the intensity, or magnitude of the abnormality in blood sugar, and the duration. Those two things clearly dictate the extent of those complications.

We now are in a position, and we have two trials actually being inaugurated at a full scale this year which will attempt to prevent hyperglycemia in individuals who are prone to develop hyperglycemia. These will have, we believe, a very dramatic effect. Given what we've learned in the Diabetes Control and Complications Trial, with a combination of drugs, lifestyle changes and using insulin in a more effective way, we believe we can affect the hyperglycemia itself once it occurs.

Furthermore, we have one additional study that has shown that we can use a drug called an ACE inhibitor, which is a drug that was formerly used for the treatment of hypertension, because it has been discovered that even when it doesn't affect blood pressure, it has a major effect on protecting the kidney from diabetic nephropathy, which is a major cause of end-stage renal disease in this country.

So we believe that we have a set of things in place that are moving forward that are going to have a very dramatic effect. For the first time, I think the Diabetes Control and Complications Trial, both in an emotional sense and a truly practical sense, put us on a course in which we really can see a light at the end of this tunnel. There are a number of other avenues that relate to islet transplantation, encapsulation of islets, crossing immune barriers and other things such as immunologic prevention of the disease in Type-I diabetes that are also very active pursuits at the present time. We're very encouraged right now about what we can do now with the technology available. Certainly we hope to have a better technology in the next several years.

CYSTIC FIBROSIS THERAPY

Mr. HOYER. Last question in this round. I mentioned the article in today's paper. I'm very involved in doing some fund-raising for what the kids call "65 roses," cystic fibrosis. In this article, the use of Motrin, ibuprofen, appears to have some really positive signs. You mentioned this with respect to the Chairman's question, but how hopeful should parents be?

Dr. GORDEN. I think it's always important in a difficult and chronic diseases like cystic fibrosis to put things in perspective. What the study shows is that the chronic deterioration of the lung can be inhibited by ibuprofen and drugs like this. It is not a cure. It will not prevent the ultimate course of this disease.

But if we can add a therapy now and it has an effect for four or five years—this study actually went for approximately four years to demonstrate the positive effect for that length of time—if we can combine these several therapies that I mentioned, and each one can have some modest effect for four years or five years, and if we can synergize these treatments, then that's actually very important news. We all remember that it was only a few years ago when very few children with cystic fibrosis reached adulthood. That is not true today. Even though the age of 30 becomes a very critical time, and only approximately half of patients will get beyond that age at the present time, that's a very dramatic change from just a few years ago.

Mr. HOYER. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Hoyer.

Mr. Bonilla.

DIABETES

Mr. BONILLA. Thank you, Mr. Chairman.

I'd like to just start out for a second, Dr. Gorden, if you'll excuse me, thanking Dr. Varmus and Mr. Williams for bearing with us for these intense hearings for so many days now. And we're finally to the last NIH hearing. We appreciate your cooperation with us for these weeks. It's been unusual, but it's been very helpful to us. And we look forward to working with you for the remainder of the year.

And also Mr. Hoyer may find it interesting, as he was kind of asking about facts and figures, but on the average, every Member of Congress has roughly 32,000 constituents with diabetes. Care for diabetics represents 14 percent of the Nation's health care bill, or $105.2 billion tabulated in 1992. So it's huge, and I'm delighted and want to associate myself with your remarks and your concerns about this problem that we're trying to address on this committee.

Diabetes, as I've mentioned and you've testified before and I've spoken to you about it over the years, has touched my family, and one of my staffer's mothers last year was diagnosed. And about three weeks ago, my district director, Phil Ricks, discovered that his blood sugar was so high on a weekend that on Monday morning the doctor ordered him to go directly to the hospital without even going by his house to get a clean shirt. He has since been stabilized and is doing much better and has drastically changed his diet and is having to give himself insulin shots for a while.

But it can hit home before you know it in many, many cases. Rest assured, that's just one story, but it's a story I'm sure so many of us can tell, it affects so many of our lives.

POLYCYSTIC KIDNEY DISEASE

I'd like to start out, Dr. Gorden, by asking about PKD, and if you could update the committee on the recent breakthroughs into polycystic kidney disease. And also, I know that this is embargoed until tomorrow, but could you give us a little hint about what NIDDK is going to announce on Friday? I'm sure, Dr. Varmus, for old times sake——

[Laughter.]

He won't mind if you tell us.

Dr. GORDEN. I imagine I could get permission to break the embargo a little bit, Mr. Bonilla. This disease, polycystic kidney disease, is the most common genetic disease of the kidney. And indeed is either one of the most or the most common genetic disease, affecting roughly half a million people in the United States. Several years ago, a locus for this gene, somewhere in the genome of the human being, was found.

Within the last two years, through somewhat of a coincidence, an intersection of two different diseases in a genetic sense allowed the discovery of what is likely to be the actual gene for this disease. What is actually being described in the next day or two is in fact the elucidation of the structure of the complete gene for what is the causative abnormality in this disease, a mutation in this gene.

With that information, we now will understand what the product of this gene is. In other words, genes themselves don't cause disease. They cause disease because they make a defective product when they are abnormal genes. We will now be able to know what this product is in its normal form, what this product does normally, and also what doesn't get done when this gene is abnormal.

So this really is a very exciting discovery. It not only offers opportunities in genetic screening, but it really offers us, for the first time, opportunities to look for ways around this particular barrier. There may be pharmacologic or other ways to treat this disease.

For instance, in an animal model of polycystic disease in the last couple of years, it was found that in young mice that a drug called

Taxol that's been used as a cancer chemotherapeutic agent, had an effect on preventing the kidney cyst formation. This gives us clues as to what this protein might be, but we still don't know exactly. We now have the opportunity to know for sure, since we do know that interventions at a very early stage can prevent this disease in animals. It gives us a great opportunity to really look for the cause of the disease in a much more direct way.

This is a very exciting and very important finding.

Mr. BONILLA. And Taxol is the one that some have raised questions about the financial profit that this drug has produced, and whether or not NIH should reap some of those profits, am I correct?

Dr. GORDEN. Yes, sir.

DIABETES

Mr. BONILLA. Let me move now to another area. I thought diabetes would be the next big disease that this Nation would cure. However, in the President's budget, it would appear that diabetes is not listed as one of the great potential research priorities for this year. What has changed that gives me concern is that diabetes might not be the next disease that we cure. Are you concerned about that now?

Dr. GORDEN. I would certainly like to see it be the next disease that we cure. I certainly think that we've made great strides in diabetes research. There is much more to be done. It's a very complex disease. Certainly, within the realm of complex diseases, such as diabetes, I think that against the chronic complex diseases we have made a considerable amount of progress that rivals much of what's happened in many other areas, such as cardiovascular, hypertensive and other diseases where there are disorders that are something like diabetes. We've been able to add some very important discoveries to current knowledge. We would like very much to see the field expand and we'd like very much to see that result in an important cure, as you suggest.

Mr. BONILLA. So should it have been listed then, in your opinion, as one of the greatest potential research priorities?

Dr. GORDEN. Well, we would like to see basically everything in our Institute listed as an important research priority. [Laughter.]

And Dr. Varmus is very much aware of that. In fact, I tell him that on a regular basis.

So we really feel that all the diseases that are an important purview of our Institute should be on the main part of the program. And we will continue to emphasize that to all who will listen.

Mr. BONILLA. Did you want to add to that?

Dr. VARMUS. I'd like to just point out, Mr. Bonilla, that we think that diabetes, among other diseases, will be among the recipients of the discoveries that will be made as a result of the initiatives we've listed. For example, there is a significant component of genetic research, including gene therapy, in the initiatives, and obviously, elucidation of the genes that contribute to both Type I and Type II diabetes, and initiatives that depend upon the development of gene therapy protocols will be addressing diabetes quite heavily.

RESEARCH GRANT SUCCESS RATES

Mr. BONILLA. Doctor, it would appear that NIDDK has many grant renewals coming due this year. Would it be correct that even if NIDDK got a 10 percent increase, the success rate for competing grants would still be lowered? And my other part of the question is, would other Institutes be faced with similar problems next year under the President's budget request?

Dr. GORDEN. In the specific case of NIDDK, our success rate in 1995 is estimated to be 25 percent. At the President's budget request in fiscal year 1996, that will drop to 18 percent, I believe. I cannot provide that information directly for all other Institutes, but I would certainly do that for the record.

[The information follows:]

EFFECT OF A TEN PERCENT INCREASE ON THE NIDDK SUCCESS RATE IN 1996

An increase in 1996 of 10% over the 1995 column of the 1996 President's Budget, which excludes AIDS research, would result in an increase of $51,593,000 beyond the request. If this amount were devoted entirely to competing research project grants, 228 additional awards could be made. This would result in a success rate for the NIDDK of 28.5% compared to the success rate of 18% for the non-AIDS portion of the FY 1996 President's Budget Request for the NIDDK.

The NIDDK's projected drop of seven points in success rate in non-AIDS research from 25% in 1995 to 18% in 1996 is a direct result of 25% success rates in both 1994 and 1995. Two comparatively good years in a row will result in higher than normal noncompeting commitments in 1996, causing a relative shortage in competing funds, although the overall research project grants program will remain strong. Other institutes which approach this drop in non-AIDS research are the National heart, Lung and Blood Institute and the National Institute of General Medical Sciences, which each drop by 4 points in success rate.

Mr. BONILLA. This cannot be something that would be desirable, under the circumstances, if you couldn't deal with all the grants that you'd like to deal with.

Dr. GORDEN. That will present a considerable difficulty.

Mr. BONILLA. What do you think we could do about this?

Mr. HOYER. Get more money. [Laughter.]

Dr. GORDEN. I certainly think that that would, I would like to reinforce your colleague's suggestion.

Mr. BONILLA. Who said that? [Laughter.]

Mr. PORTER. Would the gentleman yield?

Mr. BONILLA. I'd be happy to yield.

Mr. PORTER. Maybe, Dr. Gorden, you can tell us why it's going to drop from 25 to 18 percent. Is there a particularly large group of new grants from the previous year or what is it that's going on to make this happen?

Dr. GORDEN. That is certainly part of the issue, Mr. Porter, Mr. Bonilla. No matter how much we try, we can't avoid a certain amount of cycling that occurs between our noncompeting and competing grant portfolios. And it turns out that in fiscal year 1996 that we will have a slight increase in our non-competing grants.

While our total grant portfolio will drop by approximately 69 grants, we will have a reduction of approximately 180 in new and competing. So it disproportionately hits the new and competing because of the fact that we have a limited amount of growth, but also because of the cycling phenomenon that has to do with the noncompeting.

Mr. BONILLA. I thank you, Dr. Gorden for your appearing before us today, and look forward to working with you. I may have some more questions that I'll submit for the record, and we would appreciate your responding.

Dr. GORDEN. Thank you, sir.

Mr. BONILLA. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Bonilla.

Mrs. Lowey.

DIABETES CLINICAL RESEARCH

Mrs. LOWEY. Thank you, Mr. Chairman.

And I, too, thank you, Dr. Gorden. We appreciate the important work you're doing.

My understanding is that because of funding constraints, the testing of new therapies in diabetes generally occurs in major multi-center clinical trials supported sequentially by the NIH. Do you think there's a need to establish new diabetes clinical research programs designed to augment the existing diabetes research infrastructure? This would provide for the timely clinical testing of promising new therapeutic approaches. Shouldn't there be a mechanism for simultaneous testing of promising treatment options?

Dr. GORDEN. In trying to address this, we have suggested, Mrs. Lowey, at the present time, that it's always desirable to have specific mechanisms in which you could address a specific problem. But in the present situation, we feel that it's better to use mechanisms that we now have in existence, such as our diabetes centers, such as our prevention trials, such as our small grant mechanism for pilot and feasibility studies, and programs of this type, which we have operational now. With additional funding, we can actually use these mechanisms for that purpose.

So we don't feel at the moment that we need to establish a specific mechanism to accomplish those goals. It is absolutely critical that we respond to any opportunity for therapeutic intervention that will be significant. And we certainly are mindful of that and will certainly do that. But we do feel that we can do it with the existing mechanisms that we have in place, without a new form of mechanism.

Mrs. LOWEY. But if there were additional resources, would you consider expanding in this way?

Dr. GORDEN. We would certainly put it in a list of things that we would consider priority areas, and we would review that very carefully with our national Advisory Council so that we were putting it in an appropriate perspective with all of the other competing demands for other types of mechanisms.

Mrs. LOWEY. Do you think that the early stage clinical studies receive proper consideration in the review process at NIDDK and the NIH in general?

Dr. GORDEN. There's been a considerable concern about clinical studies. It has involved the issue of review and it has involved the issue of resources available for clinical investigation. We have tried to address those issues, and one of the things that has not always been mentioned when one reflects on clinical studies is the fact that Institutes have the opportunity to have specific reviews for specific kinds of clinical studies.

We have those forms of review mechanisms in place in NIDDK. So that if there's a very critical need to do a particular kind of clinical study, then the Institute has the opportunity and the resources, if the resources are available, to actually implement the studies, through its own review process. There are general issues still being discussed, and I think they need to be discussed, including the appropriate role for clinical research, exactly where clinical research begins and where more fundamental research takes on the characteristic of clinical research.

But I do think there are ways that we can respond to these immediate concerns, and I think that that should never be confused.

DIABETES AND CARDIOVASCULAR DISEASE

Mrs. LOWEY. Thank you.

I also want to share with you that I'm very pleased that NIDDK and the Office of Research on Women's Health will be collaborating on issues surrounding Type-I diabetic women and their increased risk of coronary death. And I understand that you will also be collaborating on detection of arteriosclerosis as a precursor to cardiovascular disease.

Are you at a point in these collaborations where you can tell us more about where they might lead us in looking at prevention and treatment of diabetes in women?

Dr. GORDEN. The issue of atherosclerotic disease or vascular disease is a very difficult issue in the whole field of diabetes. We know that heart attacks are increased by at least two-fold in diabetic individuals. We know that women, after menopause, lose their protection, we know that women with diabetes basically don't have that same cardiovascular protection, even up until the time of menopause. And we know that strokes are increased anywhere from two to five-fold in diabetic individuals.

Whether the control of blood glucose is going to have an ameliorating effect on this accelerated vascular disease cannot be stated with certainty. We only have clues in that direction. The very large cohort of patients that was included in the Diabetes Control and Complications Trial, over 1,400, are being included in a continuation trial to try to get more information about vascular disease. The issue with vascular disease is that it is much more difficult in terms of size of the study to get definitive information.

So we believe that it is terribly important to utilize all available therapeutic efforts at reducing cardiovascular risk in diabetes, and we're trying to be more specific about that. But right now, we must fall back on what we know about the general population, controlling hypertension, lipid disorders, and now hyperglycemia.

POLYCYSTIC KIDNEY DISEASE

Mrs. LOWEY. Thank you. And just following up on Mr. Bonilla's question before, I understand that the President's projected budget for fiscal year 1996 would fund only two-thirds the number of competing grants at NIDDK as are currently funded. What would a decrease of this magnitude do to PKD research and related scientific investigation?

Dr. GORDEN. Actually, that's a very good example. PKD research this year represents an enormous opportunity. We have a major discovery. This is what we mean by research being driven by opportunity. This is one of the best examples. I believe there's no way that we can retreat from an opportunity like that.

What we have done is to make a major initiative to maintain or grow the amount of the investment that we have in PKD research. We will begin that this fiscal year, because we've been aware of this progress, and we've been aware for some time of the information that will be revealed tomorrow, and we wanted to be a bit ahead of this, so that we are positioned to study this gene product, and to begin to elucidate what this gene product really means.

We put a mechanism in place to do this now, and we will certainly want to extend this until next year. Again, I'd like to reemphasize that this is really what we mean by following opportunity. This is something that always has to be the leading edge in what we're doing in funding research.

Mrs. LOWEY. Thank you.

Thank you, Mr. Chairman.

DIABETES AND STRESS

Mr. PORTER. Thank you, Mrs. Lowey.

Speaking of women with Type-I diabetes, I don't know whether I shared with you, Dr. Gorden, that my wife Kathryn has been diagnosed within the last six months as having Type-I diabetes. And her doctor mentions the role of stress in her life, like other people. Are there any studies that are being done now that take account of this factor? I know it's probably very hard to measure, right? It would seem so to me.

Dr. GORDEN. It is difficult. First of all, I'm sorry to hear that your wife has diabetes, but I'm very pleased that we can bring to the table the progress that has been made and certainly I think that her outlook is very optimistic. I'm very pleased to be able to say that, based on really objective information, rather than conjecture.

Stress has a major role in the treatment of diabetes. Certainly we know that activation of the sympathetic nervous system, which is one of the things that happens with stress, has a major effect on insulin action. In individuals who have some opportunity to secrete insulin, it has a major effect on insulin secretion. So we know in a biologic sense how certain aspects of stress can act on the disease. But we know in a broader sense that it certainly has an effect on the fluctuation of the disease with respect to treatment.

What can we do about that? We have a component of our diabetes centers called a training and translation component which is very involved in studying aspects of treatment of diabetes, such as stress.

We don't have any real answers at the present time, but we have certain kinds of modalities that we can utilize. The recognition that stress is very important in the treatment of diabetes is something that we have made an attempt to translate to the medical community and to patients. It's very important that people understand that, and the medical community understands that the stress of the disease and other stresses are very important in their own difficulty in managing their disease. I think those recognitions in the last several years have had an important impact.

DIABETES GENES

Mr. PORTER. We used to talk about the diabetes gene. And it now seems that the situation is much more complicated, that there may be multiple genes involved in different types of diabetes. Have any genetic links to the dominant forms of diabetes been established, and were we overly optimistic when we spoke of a diabetes gene initiative several years ago as being reachable in the short term?

Dr. GORDEN. I think at the time that initiative was begun it was correct. It was aimed at a complex genomic disease, because we recognize that the common forms of diabetes, Type-I and Type-II diabetes, are very unlikely to be due to a single gene defect, such as polycystic kidney disease, or such as cystic fibrosis. When that is true, we have discovered several defects. We know that the insulin receptor can have a genetic defect and cause diabetes, and we've discovered a number of diabetic syndromes that are related to that. We know that an important recognition site in the insulin secreting cell, an enzyme that recognizes glucose, can have a mutation and cause a certain form of diabetes called maturity onset diabetes of the young. And we've defined the genes that are involved in those types of abnormalities, which are excellent models for a broader search.

But within the scope of Type-I and Type-II diabetes, we now have major searches of the entire genome. For Type-I diabetes, in fact, somewhat greater progress has been made. We have found a major locus of genetic involvement. In Type-II diabetes, with the extraordinary resource of the Pima Indians that have been studied for the last 25 or 30 years, that is the major focus in this country of genetic research in Type-II diabetes. We also have a number of programs out in the community in various populations looking at so-called candidate genes.

So I think that the time for beginning to study complex genetic disorders is right. We're not as adept at studying those disorders. We don't have the technology that we do for studying single genetic disorders. But that field is moving very rapidly, and this is an appropriate time to begin those studies.

FIAU CLINICAL TRIAL

Mr. PORTER. The Institute of Medicine panel appointed to assess the conduct of the 1993 clinical trial of the anti-hepatitis drug FIAU concluded that there was no evidence of negligence or misconduct in the deaths of five participants. This is very similar to the conclusions reached by an internal NIH advisory panel.

An FDA panel, however, was much more critical of the trial. Do you think their criticisms were unjustified, and did the IOM panel make general recommendations for improving the conduct of clinical trials?

Dr. GORDEN. Mr. Porter, this has been a very tragic episode in the history of clinical research. We have enormous sympathy for the families and individuals who have been affected by this terrible tragedy. I think that the institutional response to this tragedy has really been enormous. The individuals who bore much of that burden were the individual investigators who exercised enormous courage and enormous sensitivity in responding to this emergency.

I think the NIH, Dr. Varmus, and everyone who has an institutional responsibility responded in a very effective and appropriate way. I believe and am very gratified with the conclusions of both the Directors Advisory Committee at the NIH and the IOM. I think they basically concluded the same thing that I concluded, having looked very carefully and analyzed the situation very carefully myself. And my contacts with all my clinical colleagues within the clinical center all came to the same conclusion.

I think that to some extent the FDA is dealing with a slightly different set of issues. The FDA has regulatory concerns and they're dealing with broad regulatory concerns. I think in that particular, we can always do a better job. But I think that one should listen very carefully to what the IOM committee is saying. Because what they're really saying is, yes, this has been a great tragedy, but we have to be careful that we don't become stampeded into things that may not be protective and cause a great deal of interdiction of further drug development. We have to be very careful in thinking these things through, and not respond in an immediate way to something that isn't perhaps thought out in the best possible way.

So I think that the FDA was coming at this from somewhat of a different perspective, and I think that if reasonable people sit down and talk in a reasonable way to each other that something very positive will come out of this.

DIABETES AND PUBLIC EDUCATION

Mr. PORTER. You indicate that your Institute is expanding its public education efforts in the area of diabetes. As you know, CDC has an active diabetes translation program for which this subcommittee has been increasing funding. How do you sort out an appropriate division of responsibility for diabetes public education between your Institute and the CDC?

Dr. GORDEN. CDC's role has primarily involved States and State health departments. The Diabetes Control and Complications Trial truly created for us a message that we've got to get into the public domain. So Dr. Eastman has taken up a major initiative, and a major role in collaboration with the CDC and also involving industry collaboration, so that we can make a very modest investment in catalyzing an education program.

We are reluctant to call it an education program until it matures into something that is more consistent with what the NIH has referred to as an education program. Ours is a new and somewhat embryonic program. We believe that by making a very small investment and cooperating with the CDC and allowing this to catalyze within our information network and within our diabetes program division, that this will be a very positive step and will help to create a public message much quicker than we could do through scientific medical communications alone.

Mr. PORTER. Dr. Gorden, let me thank you for your excellent testimony and your forthrightness in answering all of our questions. The subcommittee is very benefitted by your knowledge and communication of it to us. And we appreciate the job that you're doing at NIDDK and for our country. Thank you very much.

Dr. GORDEN. Thank you very much, Mr. Chairman.

Mr. PORTER. This also, I might say, concludes our hearings on the National Institutes of Health. We would like to thank Dr. Varmus for taking time from his very busy and important schedule to spend a great deal of time with us. Your being here has been very helpful, Dr. Varmus. We've discussed a lot of cross-cutting issues where you've been able to participate and bring us up to date. I know that the Members of the subcommittee, as well as the Chairman, very much appreciate the opportunity to have a dialogue with you on these very, very important issues. And we know that that dialogue will continue throughout the year. Thank you for being with us.

Dr. VARMUS. I've appreciated the chance to have this prolonged conversation.

Mr. PORTER. This also concludes our hearings on the Department of Health and Human Services, and Dennis, you have been steadfast in your attendance, along with Bill Beldon. We appreciate the work that you do also, and we know that you will continue to dialogue with us and with the staff as these budgetary questions come upon us with a vengeance in the couple of months ahead.

Thank you so much.

Mr. WILLIAMS. We always stand ready to serve.

Mr. PORTER. Thank you very much.

The subcommittee will stand in recess until 10:00 a.m. Tuesday.

[The following questions were submitted to be answered for the record:]

FUNDING FOR SELECTED DISEASE AREAS

Mr. Porter: Identify 1994-1996 spending on the following: diabetes, interstitial cystitis, obesity, prostate, inflammatory bowel disease, celiac disease, osteoporosis, nutrition, cystic fibrosis, polycystic kidney disease, Cooley's anemia, sickle cell anemia, and IgA nephropathy.

Dr. Gorden: The following table identifies spending by the NIDDK for those diseases:

(Dollars in thousands)

	1994	1995	1996
Diabetes	$191,409	$197,100	$203,100
Interstitial Cystitis	8,980	9,200	9,500
Obesity	33,200	34,200	35,200
Prostate	9,441	11,800	12,100
Inflammatory Bowel Disease	13,934	14,300	14,800
Celiac Disease	1,634	1,700	1,800
Osteoporosis	18,300	18,900	19,500
Nutrition	70,049	72,100	74,200
Cystic Fibrosis	21,889	22,500	23,100
Polycystic Kidney Disease	5,882	6,100	6,200
Cooley's Anemia	5,300	5,400	5,600
Sickle Cell Anemia	5,793	6,000	6,100
IgA Nephropathy	12,600	13,000	13,300

CENTERS

Mr. Porter: Identify the number and subject matter of research centers supported in 1995.

Dr. Gorden: The NIDDK is supporting research centers spanning nearly all of its programs in FY 1995. There are 12 diabetes centers, comprising both the Diabetes Research and Training Centers and the Diabetes-Endocrinology Research Centers. In the field of cystic fibrosis and gene therapy, the institute supports 8 Cystic Fibrosis Research Centers, including one newly started in FY 1994 at the direction of the Congress.

NIDDK supports 12 Digestive Disease Core Centers which encompass the fields of liver research, gastrointestinal research, and a center devoted to research on inflammatory bowel disease. Six Clinical Nutrition Research Units are supported, including one newly started in FY 1994 at the direction of the Congress. Four Obesity Research Centers are supported, in a field allied with both nutrition and metabolism research.

The George M. O'Brien Kidney and Urologic Diseases Centers supported by the NIDDK include nine involving kidney disease research and five involving research on urologic diseases. The field of Hematology has the newest research centers program at the NIDDK, for which short-term 7 planning awards were made in 1993, followed by a competition in 1994 in which the current three Hematology Research Centers were initiated.

INFLAMMATORY BOWEL DISEASE

Mr. Porter: What is the state of the science with regard to inflammatory bowel disease? Is it a field that needs further development or is there research that is ready to be supported but which cannot be because of fiscal constraints?

Dr. Gorden: Inflammatory bowel disease (IBD) is a general term used to refer to two diseases, ulcerative colitis and Crohn's disease. While these diseases are considered to be autoimmune in etiology, their pathogenesis is complex and not well understood. It appears that IBD is the result of such factors as genetic predisposition and alterations in the mucosal immune system, which are triggered by exposure to intestinal microbes, toxins, food substances or drugs. Current therapies are helpful in ameliorating the symptoms and complications of these diseases, but in general are unsatisfactory because they fail to provide a specific cure or to prevent or alter the eventual natural history of disease in the majority of patients. The NIDDK is intensifying its research effort into defining the pathogenesis of IBD to foster prevention and therapy of these important gastrointestinal diseases. The Institute is encouraging collaborative research among the multiple disciplines of gastroenterology; immunology; epidemiology; physiology; molecular, structural, and cell biology; and genetics. To stimulate this research, the Institute is attempting to use all appropriate mechanisms, including individual R01 and P01 grants, planning grants, training grants, center grants and support of research workshops. It especially encourages new investigators from different areas of research to apply cutting edge research technology and innovative approaches to the understanding of these diseases. Since 1989, owing to special congressional emphasis on IBD research, the NIDDK investment has grown by close to 300 percent. The NIDDK will continue to stimulate further research activity in IBD with the anticipation of funding as many highly meritorious applications as is possible within available resources.

OBESITY

Mr. Porter: On March 9th, The New York Times reported a study that found that a person's metabolism adjusts to maintain a "natural weight," eventually offsetting weight loss. In the field of obesity research, I am sure researchers are very interested in this finding because it helps to explain recidivism in weight loss programs, but isn't this fairly pessimistic news for those who are trying to lose weight? What leads does this suggest for the treatment of obesity?

Dr. Gorden: I actually draw an optimistic message from the study you have mentioned, which was conducted by NIDDK-supported researchers. It represents one of the most careful and thorough investigations of this question that has ever been done. The results are clear in demonstrating that, if you take a person who is at a stable weight, whether he or she is thin or fat, and try to change that weight, the body will attempt to compensate by altering its non-resting metabolism in a direction to return to the original weight. Understanding this mechanism of weight stabilization, or "set-point," is the first step to devising ways to alter it.

We already have a number of clues about the factors that affect the set-point for body weight. Past studies have identified ongoing physical activity as the single best predictor for whether individuals who have lost weight will be able to maintain their weight loss. It seems likely that the set-point for body weight can be lowered by increasing physical activity levels. It also may turn out that composition of the diet, for instance, fat content, may help to determine the level at which the body regulates its weight. The NIDDK is actively pursuing these research questions.

Another concept I would like to stress is the need to focus on an individual's overall health and metabolic fitness, regardless of absolute weight. For instance, in diseases such as diabetes it is possible that small reductions in weight and sustained increases in physical activity may lead to large overall improvements in health and well-being. A major clinical trial, the Diabetes Prevention Program, will be testing this strategy in the prevention of non-insulin dependent diabetes mellitus in individuals at risk for developing the disease.

There has been an epidemic in obesity in the U.S. over the past 10 years. Clearly, if there is a natural set-point for each person, this point must have changed in many people over the decade to account for the 30 percent increase in obesity that we have seen. This increase reflects complex interactions between different genetic backgrounds, unhealthful individual lifestyles, and a societal environment that encourages physical inactivity and poor food choices. Determining the factors that influence food choices and level of physical activity will enable us to design targeted strategies to prevent obesity in high-risk individuals and groups, as well as in the general population. I believe that prevention of obesity would have a major impact on many chronic diseases, offering enormous potential for benefits to society, both in individual well-being and in decreased health care costs. NIDDK will continue to take the lead in supporting obesity research studies at all levels, from molecular genetics to clinical treatment and prevention. We also have established the Weight Control Information Network, or WIN, to help translate our scientific discoveries into practical advice for the public.

Mr. Porter: The recent finding of a gene in a mouse model that is related to obesity seems to offer more promise to those who are overweight. Is any translation of this research into treatment options likely in the next few years?

Dr. Gorden: The discovery of the *ob* gene by NIDDK-funded researchers is truly a breakthrough event in obesity research. This gene makes a protein that appears to play a crucial role in control of weight in mice. In normal mice, the *ob* gene apparently is "switched on" in fat tissue, generating a specific protein product. Researchers believe that this protein enters the bloodstream and travels to the brain, where it acts on the appetite-controlling region to regulate food intake and/or energy expenditure. When the gene is mutated, these control mechanisms don't work properly, and the mouse becomes grossly obese, often developing diabetes.

Most exciting is the fact that investigators have identified a human gene that is very similar to the mouse *ob* gene, and is likely to perform similar functions in humans. The NIDDK is moving very rapidly to cooperate with the research community in following up on this crucial discovery. We will be holding a workshop in August to bring together researchers in this field to help coordinate the next steps. The NIDDK also has provided supplemental funding to several investigators to rapidly follow-up on the possible role of the gene in humans. I would like to acknowledge that the Office of Research on Minority Health at NIH is providing funds to help us in this effort, so that we can look at the occurrence of this gene across different human populations.

I am hopeful that these findings will lead to dramatically more effective biological therapies for weight control that are based on molecular knowledge of specific obesity gene proteins and how they relate to the mechanisms of satiety and energy expenditure. The discovery of the *ob* gene research also may give us the ability to test early in life for the genetic predisposition to at least some forms of obesity. Individuals found to be at risk could be helped to adopt healthy behaviors in order to prevent the onset of obesity. The fact that the biotechnology industry already has licensed the rights to develop the gene product reflects the importance of this discovery.

TYPE II DIABETES

Mr. Porter: Can you explain the potential significance of the recent finding that overproduction of a protein may be linked to Type II diabetes?

Dr. Gorden: Insulin resistance is a cardinal feature of non-insulin-dependent diabetes mellitus (NIDDM), or Type II diabetes. It occurs when individuals produce a normal amount of insulin, but the body is unresponsive or resistant to the action of the insulin to regulate blood sugar levels. We know that insulin receptor molecules, which normally are present on the surface of cells, are responsible for binding insulin. When this process occurs successfully, enzymes are triggered that promote growth and cell survival. Interestingly, NIDDM patients tend to have normal insulin genes, receptors, and enzyme systems, so scientists have long wondered what is the actual cause of insulin resistance. Now, NIDDK-supported researchers have found that a protein, called PC1, is present in ten times the normal amount in a large proportion of individuals with NIDDM. They speculate that overabundance of PC1 may somehow be involved in impairing the function of the insulin receptor, thereby causing cell resistance to insulin, which causes NIDDM. Further investigations are required to determine the role of PC1 in diabetes. If it is in fact important in the development of NIDDM, it would be a target for new drugs which might block PC1 and normalize cell activity.

CYSTIC FIBROSIS

Mr. Porter: Your Institute has the lead throughout NIH on cystic fibrosis research. Can you tell us what your recently established cystic fibrosis gene therapy centers are contributing to the field? Have they found any answers to the problems of finding suitable carriers for the gene therapy?

Dr. Gorden: Since the cloning of the gene responsible for cystic fibrosis (CF), development of safe and effective methods of gene therapy has become a major goal of CF research. In 1993 and 1994, the NIDDK funded the first three NIH research centers for gene therapy of CF and other genetic diseases. Phase One clinical trials of gene therapy directed to the airways of CF patients are now under way at NIDDK CF gene therapy centers at the University of Pennsylvania and the University of Washington. Both centers are using first-generation adenoviral gene carriers, or vectors, in which deletion of viral genes render the virus incapable of replicating. To alleviate problems with inflammation and transient gene expression encountered with this vector, research is now focused on development of an adenoviral vector which is further crippled to prevent viral protein expression. Development of other methods of gene therapy are also under way. Adeno-associated virus is a nonpathogenic virus that appears promising for therapy of CF. Much of the early characterization of this vector was done in the NIDDK intramural program and its further development is now a focus of our gene therapy center at the University of

Washington. Use of liposomes as vehicles for gene therapy of CF is a major focus of research at our gene therapy center at the University of California at San Francisco. Liposome and adeno-associated virus vectors have been studied extensively in animals, and it is likely that Phase One clinical trials with these vectors in patients with CF will begin in the next few years.

WEIGHT-CONTROL INFORMATION NETWORK (WIN)

Mr. Porter: According to a recent study by the National Center for Health Statistics, the number of overweight adults, which had remained stable at about 1/4 of the adult population from 1960 through 1980, suddenly jumped to 1/3 of all adults between 1980 and 1991. [Obesity was defined as being 20% or more above a person's desirable weight.] Tell us more about your new outreach program - the Weight-Control Information Network - and how it proposes to tackle this national problem.

Dr. Gorden: To address the growing rates of obesity, NIDDK established the Weight-Control Information Network (WIN) in June 1994. Authorized by P.L. 103-43, WIN is a national source of information, for health professionals and the public, on weight control, obesity, and weight-related nutritional disorders.

WIN produces, collects and disseminates fact sheets and pamphlets, journal article reprints, and literature searches on a variety of topics such as "Understanding Adult Obesity" and "Nutrition and Your Health: Dietary Guidelines." The National Task Force on Prevention and Treatment of Obesity provides expert advice to WIN, which supports and disseminates the position papers and journal articles produced by the Task Force.

To encourage at-risk people to achieve and maintain a healthy weight, WIN is developing communication strategies through a pilot program at NIDDK's Obesity/Nutrition Research Center at New England Medical Center in Boston, Massachusetts.

INFLAMMATORY BOWEL DISEASE

Mr. Porter: I understand that more than one million people in the U.S. suffer from inflammatory bowel disease -- IBD. What types of research are you supporting in this disease area? Do you anticipate any advances in the near future in the treatment or prevention of IBD?

Dr. Gorden: We are currently funding research in IBD that is investigating the following areas: the intestinal epithelial response to inflammation, the regulation of immunosuppressive molecules in IBD, a transgenic rat model of IBD, neoplastic complications of IBD, the cytoprotective role of heat shock proteins in IBD, the role of nitric oxide in colonic inflammation, the autoimmune mechanism in ulcerative colitis, and immunoregulatory bacterial factors in ulcerative colitis. New research findings in the area of inflammatory bowel disease are steadily emerging to significantly advance the field toward prevention and treatment of IBD. One such example is the development of new animal models known as "knockout" mice, which will help us understand drug mechanisms and lead to possible treatment options. To illustrate, recent studies have provided new insights into how one particular drug acts to counter the immune injury that is observed in IBD. These animal models should not only generate new concepts about the role of inflammatory mediators in the intestine, but also help us to apprehend the genetic and environmental influences that determine susceptibility to this disease. Thus, we are developing an impressive base of research on IBD.

POLYCYSTIC KIDNEY DISEASE

Mr. Dickey: What recent advancements have been made in the area of polycystic kidney disease?

Dr. Gorden: This year, polycystic kidney disease (PKD) researchers attained a long-sought goal: the identification and the sequencing of the PKD1 gene. The search for this gene was set in motion by NIDDK-supported studies that, in 1985, linked the genetic mutations in PKD to a region (the "PKD1 locus") of chromosome 16. That search led to the identification this year of a defective gene, at the PKD1 locus, by the European PKD Consortium and to the sequencing of the full gene by the American PKD Consortium, including NIDDK grantees at The Johns Hopkins University. Incomplete understanding of the gene has been a major limitation in research to develop effective PKD treatments. Its sequencing should now make it possible to determine the normal role of the PKD1 protein in the cell and the mechanisms by which gene mutations cause the human disease.

NON-INSULIN-DEPENDENT DIABETES

Mr. Dickey: How has your research of diabetes improved the ability to detect non-insulin-dependent diabetes mellitus at an earlier stage of the disease?

Dr. Gorden: There appear to be four major stages in the development of non-insulin-dependent diabetes mellitus (NIDDM): Genetic susceptibility; hyperinsulinemia and/or insulin resistance; impaired glucose tolerance (IGT); and, finally, NIDDM. A few genes that correlate with susceptibility to NIDDM have been identified in certain families and populations. These genes in total, however, do not account for a proportion of NIDDM large enough to be useful in general screening for susceptibility to NIDDM. There are tests for detecting insulin resistance and IGT, the two pre-diabetic states; positive tests are predictive of NIDDM. Generally, however, these tests are performed either in a research setting on individuals at increased risk for developing diabetes, or to confirm a diagnosis of NIDDM. Research is progressing toward being able to make available to the general population diagnostic tests for susceptibility to NIDDM and for the pre-diabetic state.

There is another point about NIDDM that I would like to make. There are several known environmental determinants of NIDDM which provide a basis for preventing NIDDM. For example, next to aging (which we can't do much about), obesity is the single greatest risk factor for developing NIDDM. Physical inactivity is another major risk factor. We know that obesity prevention, weight normalization in obese diabetics, and physical activity and exercise are very important in reducing the incidence of NIDDM. The NIDDK is supporting a host of studies that will lead to understanding precisely how NIDDM may be prevented.

JUVENILE DIABETES

Mr. Dickey: What advancement has NIDDK made in the area of juvenile diabetes?

Dr. Gorden: The most exciting and important of our many advances is the Institute's landmark Diabetes Control and Complications Trial, which showed that very careful management of blood glucose levels dramatically reduces the risk of life-threatening complications -- eye, kidney, and nerve damage -- due to juvenile diabetes, also known as insulin-dependent diabetes mellitus (IDDM). Subsequently, we have initiated efforts to disseminate, evaluate, and investigate these results.

In addition, NIDDK-supported research has revealed that: Coxsackie virus may trigger the initiation of IDDM in humans; in a small pilot clinical study, individuals at high risk for IDDM could be "vaccinated" to prevent IDDM; artificial insulin-producing cells can be created by genetic engineering; and insulin-producing cells can be encapsulated within artificial membranes and then be implanted in animals and humans, where they supply insulin to the body.

GENETIC CAUSES OF DIABETES

Mr. Dickey: What is NIDDK doing to find more information on possible genetic causes of the forms of diabetes?

Dr. Gorden: Intensified genetics research offers great promise for understanding, controlling, and preventing diabetes. Over the past several years, the Institute has developed a major initiative to encourage research on the genetics of diabetes and the search for diabetes genes. This initiative includes 15 regular research grants awarded from two separate requests for applications (RFAs), and many investigator-initiated regular research grants. In FY 1994, the NIDDK funded research on the genetics of diabetes at a level of approximately $28.3 million. The Institute continues to enhance support for both the basic understanding of diabetes and for the direct application of this knowledge to the clinic.

DIABETES PREVENTION AND TREATMENT INITIATIVE

Mr. Dickey: What results, if any, have you already received from the Diabetes Prevention and Treatment Initiative?

Dr. Gorden: The two major activities of this initiative are the clinical trial to prevent insulin-dependent diabetes, the DPT-1, and the clinical trial to prevent non-insulin-dependent diabetes, the Diabetes Prevention Program (DPP). Both trials were begun only within the past year. The first patients recently were recruited and enrolled in the DPT-1, and the trial protocol is near completion for the DPP. Patient recruitment has not yet begun for this trial. In that the DPT-1 and DPP are scheduled to run for 5 and 7 years, respectively, we do not expect results to be made public for some time.

GENE THERAPY

Mr. Stokes: The congressional justification indicates that with respect to gene therapy, gene identification is only the first step toward the development of gene therapy for the treatment of disease, and that techniques must be refined before they can be used widely to treat disease. To what extent are we making progress in our ability to expedite the refining, and what diseases under the purview of your institute are good candidates for gene therapy? In which diseases are we having the most success in applying gene therapy?

Dr. Gorden: In order for gene therapy to be effective, genes need to be delivered to the appropriate cell within the body and they need to produce their product continuously at physiologically appropriate levels. The method most commonly used to deliver genes to cells has been to modify viruses by deleting viral genes and replacing them with therapeutic genes. Progress has been made in this technology and several viral vectors are being evaluated in humans for safety and efficacy. The best studied viral delivery system, based on retroviruses, can induce long-term gene expression but is very inefficient. In an NIDDK supported study, retroviruses have been used to deliver the low-density lipoprotein receptor gene to the liver of patients with the most severe genetic form of hypercholesterolemia. The corrected gene was expressed for over a year but only a few percent of the liver cells were corrected. However, even this low level of expression produced a significant decrease in the patients' serum cholesterol levels.

The feasibility of gene therapy for Cystic Fibrosis is strongly supported by the demonstration that transduction of the normal CF gene into cells from CF patients corrects the defect in chloride transport that is the hallmark of CF. Vectors based on adenovirus are being evaluated for the treatment of CF in a number of clinical trials. While this vector is very efficient at transducing cells with the CF gene, the gene expression is transient. Studies are ongoing to see if the duration of expression can be extended by improving the vector to reduce the immunological response to the viral proteins. In addition, two other trials are awaiting FDA approval for cystic fibrosis: one using a nonpathogenic virus, AAV, which is capable of long-term expression and another using liposomes to deliver the normal CF gene.

The NIDDK is supporting two gene therapy trials for Gaucher Disease which have received final approved by the RAC and the FDA. In these trials, bone marrow stem cells will be isolated from the blood, transfected with a retrovirus containing the glucocerebrosidase gene and returned to the patient. These studies will determine if progenitor cells can be transduced which could repopulate the blood with genetically corrected cells. If this strategy is successful, it can be applied to many diseases in which bone marrow transplantation is curative such as sickle cell anemia, thalassemia, adenosine deaminase deficiency and mucopolysaccharidosis.

Progress has been achieved in delivering genes using several strategies. Further improvements are clearly needed to make gene therapy a reality for the treatment of genetic diseases. Improvements in the ability to target genes to the appropriate tissues so that gene can be delivered directly to the patient are needed. The NIDDK supports Gene Therapy Centers for Cystic Fibrosis and Other Genetic Diseases and Centers of Excellence in Molecular Hematology where the problems of gene delivery and extended gene expression are the major research focus.

DIABETES

Mr. Stokes: Approximately 14 million Americans suffer from diabetes, and nearly half of them are not even aware that they have the disease. The Justification indicates that diabetes is the leading cause of adult blindness, kidney failure, non-traumatic amputations, and is a major risk-factor for stroke, heart attack, and premature death. Doctor, this is a very bleak picture. African Americans and Hispanics suffer disproportionately higher rates of this devastating disease. Are we making any significant progress in the treatment, early detection, and prevention of diabetes?

Dr. Gorden: Yes, Mr. Stokes, we are. The NIDDK recently initiated a major clinical trial of diabetes prevention strategies targeted at individuals with known risk factors for non-insulin-dependent diabetes mellitus (NIDDM) and/or newly diagnosed NIDDM. Minorities will make up at least 50 percent of the study population, and interventions will include diet, exercise, and/or drugs. In this new initiative, the NIDDK is collaborating with the NIH Office of Research on Minority Health and the National Institute of Child Health and Human Development. The NIDDK also has begun an initiative entitled "Intervention Studies in Diabetes Among Minority Populations," which will broaden understanding of the cause, course, diagnosis, treatment, cure, and prevention of NIDDM and its complications among African, Asian, Hispanic, and Native Americans, as well as Alaska Natives, Pacific Islanders, and Native Hawaiians. The NIDDK and the NIH Office of Research on Minority Health are collaborating on a clinical study of the development of NIDDM in Mexican-American Women, aimed at identifying early metabolic defects in women at high risk for NIDDM because of prior NIDDM associated with pregnancy. In future studies, these early defects may be targeted for interventions aimed at delaying or preventing the onset of NIDDM.

This has been an exciting year for diabetes research in general. Research has provided growing evidence that NIDDM, which generally appears in middle age, is largely a preventable disease. Several studies have demonstrated the protective effects of regular exercise and healthful eating in people at risk for NIDDM. It has also been shown that a drug, called troglitazone, improves the two conditions that give rise to NIDDM -- impaired glucose tolerance and insulin resistance -- and hypertension in obese, but not yet diabetic, individuals. Thus, troglitazone may be of potential benefit in preventing NIDDM. In addition, the Food and Drug Administration recently approved a new drug for the treatment of NIDDM. This drug, called metformin, increases the body's response to its own insulin, and only rarely causes the hypoglycemia and weight gain that alternative oral diabetes drugs do.

Because genetics appears to be the common denominator underlying the various factors that lead to diabetes, intensified genetics research offers promise for understanding, controlling, and preventing diabetes. Candidate genes are being identified and their specific roles are being studied, with the hope of learning more about how and why diabetes develops and which genes and gene products would be promising targets for treatment.

The early detection of NIDDM, particularly before an individual becomes diabetic, is a challenging problem. There appear to be four major stages in the development of NIDDM: Genetic susceptibility; hyperinsulinemia and/or insulin resistance; impaired glucose tolerance (IGT); and, finally, overt NIDDM. A few genes that correlate with susceptibility to NIDDM have been identified in certain families and populations. These genes in total, however, do not account for a proportion of NIDDM large enough to be useful in general screening for susceptibility to NIDDM. There are tests for detecting insulin resistance and IGT, the two pre-diabetic states; positive tests are predictive of NIDDM. Generally, however, these tests are performed either in a research setting on individuals at increased risk for developing diabetes, or to confirm a diagnosis of NIDDM. Research is progressing toward being able to make available to the general population diagnostic tests for susceptibility to NIDDM and for the pre-diabetic state.

Mr. Stokes: Is there targeted research and outreach underway to address the disease in Americans that are at high risk for the disease?

Dr. Gorden: In addition to the targeted NIDDK research efforts I have just described, some of our Diabetes Research and Training Centers (DRTCs) include outreach programs for minority populations. The DRTCs have a component in training and information transfer. This component focuses on the training of health and allied health professionals. The goal is to transfer newly developed information relevant to diabetes care to current medical practice. This goal was proposed in 1975 by the National Commission on Diabetes, which was clear in its assignment to DRTCs that the centers should *"Translate the advances in the field of diabetes research with least delay into improved care for the diabetic [patient] in the setting of model patient care demonstration units within the Centers and through outreach programs to the regional community."* The translation of new science to patient application would occur automatically and spontaneously if it were not for the existence of a variety of barriers impeding the process. These barriers include (1) geographic distance, (2) communication failures, (3) existing attitudes and beliefs, (4) reimbursement issues, (5) lack of message clarity, (6) lack of message utility, and (7) political and social issues. One purpose of the DRTCs is to find ways, through research, of overcoming these barriers.

By way of example, the DRTC at The University of Michigan (MDRTC) conducts The Preconception Project, which involves diabetic women receiving their preconception and obstetrical care at various hospitals. This program initially was not specifically targeted for minorities, but the patient population at two of the hospitals, Hutzel and Henry Ford, have a very high minority percentage, so that the percentage of minority women in the project is much higher than the percentage of minority women in the state of Michigan generally.

The Coalition for Diabetes Education and Minority Health has three members from the MDRTC. Upward of 95 percent of the African Americans in Michigan are located in Detroit so that the functional characteristic of the Coalition is Detroit-based. The Coalition is a cooperative of several agencies with an interest in diabetes. The MDRTC is a major participant in the Coalition's activities.

The Minority Committee of the Michigan Affiliate of the American Diabetes Association also has important membership from the MDRTC and, again, because of the distribution of minorities in the state of Michigan, most of the activities of this committee are directed at Detroit populations.

Another of the NIDDK's outreach programs is the National Diabetes Information Clearinghouse (NDIC). The NDIC has compiled a directory of programs and other resources to help health educators, public health officials, community leaders, and others in developing educational programs to foster awareness of diabetes and its management among African Americans. The directory, *Diabetes-Related Programs for Black Americans: A Resource Guide*, includes descriptions of diabetes-related programs that are targeted to African Americans or that serve communities with substantial African American populations. In addition, the NDIC distributes a listing of Spanish-language diabetes education materials available from a variety of sources. It also offers a number of Spanish-language publications, including a dictionary of diabetes-related terms and brochures about periodontal disease and diabetes.

The NDIC also will distribute a Spanish-language publication on the results and recommendations of the NIDDK's recently completed, and very successful Diabetes Control and Complications Trial.

Mr. Stokes: African Americans and Hispanics also suffer an increased number of amputations from this disease as compared to the general population. Would you explain why, and outline what is being done to address this problem?

Dr. Gorden: Diabetes is the leading cause of lower extremity amputations (LEAs) in the U.S., accounting for approximately 50 percent, or 60,000, of all nontraumatic LEAs each year. Peripheral neuropathy resulting from diabetes may result in loss of sensation in the feet and the development of foot deformities; these deformities, in turn, can cause pressure points that may ulcerate. Inadequate blood supply and infection may then result in osteomyelitis and gangrene that necessitate LEA.

The risk for LEAs within the population with diabetes increases by age and by the duration of diabetes. Because certain minority groups have a higher prevalence of non-insulin-dependent diabetes than the general population, they also have a higher prevalence of complications from diabetes, including neuropathy and LEAs. In the U.S., it is estimated that 44 to 85 percent of LEAs among persons with diabetes can be prevented with improved foot care programs. This will require that primary care physicians implement preventive programs within their practices, as the majority of individuals with NIDDM are cared for in the community, not at large clinical or academic centers. Clinicians will need to provide patients with information about proper foot care and the need for daily foot inspection, as well as intensified collaboration among medical and public health practitioners. One model program that appears to be reducing the incidence of LEAs is in the State of Washington. State and county surveillance data developed by the Washington State Department of Health assist public health practitioners and health-care providers in directing services to the populations with greatest need. The State's diabetes control program then provides community health centers and hospitals with educational materials and technical assistance to prevent diabetes-related LEAs.

Mr. Stokes: Is there a national plan that is designed to accelerate research in diabetes, and if not, why not?

Dr. Gorden: The NIDDK has developed a planning process that, over the past ten years, has set a framework for guiding future Institute program activities. Each year, this process culminates in the presentation and discussion at the September meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council of a planning document called the "Program Plan."

The Plan contains concepts for new or expanded program initiatives for the coming fiscal year. The initiatives would pursue some of the most promising scientific research opportunities in areas under the purview of the NIDDK; over 60 such initiative concepts are described for FY 1995.

The NIDDK's program planning process is continuously evolving and is predicated on wide-ranging and continuous collaboration between the NIDDK and non-Federal scientists and other advisors, including the Institute's National Advisory Council and sub-councils, and Division advisory groups. Input is also received from NIDDK-sponsored workshops and conferences, and through other mechanisms. Initiative concepts in the Program Plan build on past accomplishments and reflect emerging scientific needs and opportunities; are responsive to the changing fiscal environment and new Congressional and Administration directives; and are consistent with the NIDDK's commitment to investigator-initiated research.

Except for rare circumstances in which Congress or the Administration mandates a specific research effort, the NIDDK does not direct research. The planning process is intended to facilitate, not direct, research. Indeed, most biomedical research results from decisions made by researchers in the field and peer review committees--of which the National Advisory Council is a vital part. Generally, scientific merit and feasibility, as well as the intensity of research grant applications in a given field, provide the greatest impact on research developments and management decisions.

Mr. Stokes: How much is included in the FY 1996 budget for diabetes research, and how does this compare to FY 1995 and FY 1994?

Dr. Gorden: The budget for diabetes research in FY 1996 for the National Institute of Diabetes and Digestive Diseases is approximately $203,100,000. This compares to an estimated amount of $197,100,000 in FY 1995 and an actual amount of $191,409,000 in FY 1994.

For the total National Institutes of Health, the budget for diabetes research in FY 1996 is approximately $313,490,000. This compares to an estimated amount of $303,940,000 in FY 1995 and an actual amount of $293,615,000 in FY 1994.

INSULIN RESISTANCE

Mr. Stokes: Yesterday's Washington Post carried an article entitled "Deciphering Diabetes." It stated that unlike people with Type 1 diabetes, People with Type 2 diabetes do make insulin. The problem is, the insulin doesn't work the way it is supposed to. How extensive is this and what causes insulin resistance in diabetes? Are we making any progress in this research area?

Dr. Gorden: Insulin resistance is a hallmark of Type 2, or non-insulin-dependent diabetes mellitus (NIDDM). It actually first occurs in the pre-diabetic state, when individuals produce a normal amount of insulin, but the body is unresponsive or resistant to the action of the insulin to regulate blood sugar levels. Insulin receptor molecules, which normally are present on the surface of cells, are responsible for binding insulin, at which point enzymes are triggered that promote growth and cell survival. NIDDM patients, however, tend to have normal insulin genes, receptors, and enzyme systems, so scientists have long wondered what is the actual cause of insulin resistance. Now, NIDDK-supported researchers have found that a protein, called PC1, is present in ten times the normal amount in a large proportion of individuals with NIDDM. They speculate that overabundance of PC1 may somehow be involved in impairing the function of the insulin receptor, thereby causing cell resistance to insulin, which causes NIDDM. Further investigations are underway to determine the role of PC1 in diabetes. If it is in fact important in the development of NIDDM, it would be a target for new drugs which might block PC1 and normalize cell activity.

OBESITY

Mr. Stokes: Obesity is a major contributing factor in a number of diseases and disorders. In fact, the media has been giving increased attention to this health problem. What are the latest research findings in this area, and what are their implications?

Dr. Gorden: I believe that these fundamental findings will benefit all individuals with weight control problems, including minority women with obesity. In a breakthrough discovery this past year, an obesity gene was identified in mice that appears to have a human counterpart. We think this gene produces a protein that signals the brain about satiety and fat storage. It should teach us a great deal about these two areas and perhaps lead to more effective biological therapies for obesity, based on this molecular knowledge. In fact, industry has already bought the license to develop the protein product of the newly discovered gene.

An NIDDK-funded study also has shown that an individual's body, whether fat or thin, tends to stabilize at a certain weight and then adjusts its non-resting metabolism to resist changes up or down. Over one third of the participants in that study were minorities, and the phenomenon was the same regardless of race or ethnicity. We are now concentrating research on ways to readjust metabolism, satiety, and other factors that are found to be involved in excessive weight gain. We also are focussing on improving an individual's metabolic fitness, regardless of absolute weight. It may be that fairly small changes in weight, eating habits, or physical activity can lead to important improvements in metabolic factors associated with diabetes, cardiovascular disease, and other complications of obesity. Our ultimate research goal is the prevention of obesity. Towards that end, the NIDDK has set up an outreach program to provide the public with the latest science-based information about obesity treatment and prevention. It is called WIN: the Weight Control Information Network.

KIDNEY FAILURE

Mr. Stokes: Are we seeing a decline in kidney failure, and if not, why not?

Dr. Gorden: According to the latest report of the NIDDK-funded U.S. Renal Data System, the prevalence of end-stage renal disease (ESRD) increased approximately 11 percent between 1990 and 1991, continuing a trend that has yielded a 9 to 13 percent increase in prevalence counts each year since 1984. Patients between 20 and 64 years of age continue to represent the majority of patients treated for ESRD in the U.S. However, the prevalence rates have increased at an even greater than average rate for patients in the 65-74 and the 75-years-and-older age groups. ESRD due to diabetes and hypertension, the leading causes of ESRD, also increased at a greater than average rate. Diabetes and hypertension therapy has significantly improved patient longevity. The U.S. population is also aging, and diabetes and hypertension are more common at older ages. In addition, there is a direct correlation between the length of time an individual has diabetes or hypertension and the risk of end-stage kidney failure. Thus, the aging U.S. population and longer survival rates for diabetes and hypertension are probably two major reasons that the prevalence of ESRD has increased so dramatically. It has also been suggested that a larger proportion of people over 65 years of age are seeking treatment for ESRD. The aim of our research is to arrest the upward trend in the prevalence of ESRD through the development of innovative approaches to prevent and treat kidney diseases so that they do not reach end-stage.

Mr. Stokes: African Americans are disproportionately represented in the dialysis population, are we making any progress at reducing the incidence of end-stage renal disease?

Dr. Gorden: We have approached this problem by encouraging research on the underlying mechanisms of renal failure in African Americans and by developing clinical intervention trials. We are initially focusing on the kidney disease of diabetes mellitus (KDDM) and hypertension-associated kidney disease. Kidney disease associated with hypertension is the leading cause of end-stage renal disease (ESRD) in African Americans. The NIDDK is conducting a clinical trial to determine whether lower than usual blood pressure control and/or certain classes of antihypertensive drugs can slow progression of kidney disease in African Americans. The full-scale phase of this African American Study of Kidney Disease and Hypertension (AASK) was launched in July 1994. It is a 7-year trial, scheduled to end in the year 2001. The NIH Office of Research on Minority Health also provides support for the AASK clinical trial, which includes more than 20 centers and involves all U.S. African American medical schools and most major metropolitan hospitals with a large African American patient population.

An important basic research advance this year was the identification of a gene that may eventually help in the development of therapies for hypertensive kidney disease in African Americans. Abnormalities in the gene lead to increased sodium reabsorption in the kidney. Because increased sodium reabsorption is associated with many types of hypertension, this gene is a strong candidate for involvement in the more common forms of hypertension. It may be of particular significance in African Americans because their hypertension is greatly aggravated when sodium is retained by the kidney.

DIABETES RESEARCH PLAN

Mr. Stokes: I understand that the National Diabetes Research Coalition has developed a white paper which outlines the extent of the diabetes problem and provides an action plan to address the disease. Are you aware of this document and if so, in your professional judgement, does it adequately address this national health problem?

Dr. Gorden: Yes, Mr. Stokes, I am aware of this document. Many scientific leaders in the diabetes community developed these recommendations in a collaborative planning effort. The level of additional funding recommended would nearly double the Institute's diabetes research effort and clearly would have an enormous impact on the pace of this research, on our understanding of processes that lead to diabetes, and ultimately on our ability to prevent, treat, and possibly cure diabetes. In this regard, the field of diabetes research is ripe with scientific opportunities. For example, in addition to the major clinical trials we are supporting to prevent diabetes, our Diabetes Prevention and Treatment Initiative includes programs to expand research on beta cell replacement therapies, on approaches to achieving euglycemia in diabetes, on the epidemiology of diabetes intervention and complications, and on diabetes prevention studies in minority populations.

Other diabetes initiatives that could be explored or expanded include: the genetics of diabetes, metabolic staging of non-insulin-dependent diabetes mellitus, the *National Diabetes Outreach Program*, kidney disease of diabetes mellitus, obesity and diabetes, and, of course, an expanded emphasis on basic, fundamental research on diabetes.

MINORITY HEALTH

Mr. Stokes: Many of the diseases under the purview of your Institute disproportionately affect minorities. To what extent is there a collaborative relationship between your Institute and the NIH Office of Research on Minority Health?

Dr. Gorden: The NIDDK has a very active collaboration with the NIH Office of Research on Minority Health (ORMH), which greatly enhances support of research in diseases that disproportionately impact the health of minorities. In diabetes research, the ORMH portfolio includes component studies of the NIDDK Diabetes Prevention Program, which focuses on preventing diabetes in minority populations. Included in ORMH support is a study on gestational diabetes mellitus (GDM) in minority women with a history of GDM and, the New Mexico

Clinical Center focusing on Native Americans and Mexican Americans. The ORMH supports a community-based Zuni Indian youth project, as well as, a family-centered diabetes project for Pueblo Indians, diabetes research in urban Indian youth, and a community-based patient education and group support project for diabetic Hispanics and their families. The ORMH supports a study on the pathogenesis of diabetes in Mexican American women to elucidate the causes of and risk factors for diabetes in this population. Further, the ORMH has provided funds to the NIDDK for the support of a portfolio of research projects on the genetic aspects of the basis of diabetes in minority populations and the underlying mechanisms controlled by gene expression. These studies include African Americans, Hispanics, Native Americans, Mexican Americans, and Native Hawaiians.

In obesity research, the ORMH supports a component of a larger NIDDK study on long-term outcome of obesity treatment in middle-aged obese African American women. This research is testing the hypothesis that weight-control intervention for middle-aged African American women will reduce body weight by five to ten percent. The study hopes to improve the outcome of obesity treatment in African American women, and in so doing, reduce the risk for diabetes.

In kidney disease research, support from the ORMH has greatly facilitated increased involvement of Historically Black Colleges and Universities, medical schools, and minority investigators in the "African American Study of Kidney Disease and Hypertension." Also, the ORMH has provided supplemental funding to NIDDK-supported projects related to sickle cell disease.

CLINICAL TRIALS

Mr. Stokes: Clinical trials are the backbone for bridging basic research and advances in medical treatments. NIH clinical trials have yielded significant health benefits for the American people and has yielded comparable economic savings as well. What are the four most significant clinical trials that are currently under way at your Institute, and what are the expected benefits to be achieved? What level of funding is included in the FY 1996 budget for clinical trials? How many trials would be funded? How many of these trials are new and how many are ongoig?

Dr. Gorden: Now that the Diabetes Control and Complications Trial, or DCCT, has been completed and the resulting findings and health message on the benefits of tight control of blood sugar level are being actively transmitted to physicians and the public, our attention has turned to primary prevention of diabetes. Two clinical trials are getting under way--one on the prevention of insulin-dependent diabetes and the other on the prevention of non-insulin dependent diabetes. There is evidence from cost-effectiveness models that prevention strategies will result in economic savings, in addition to preventing or delaying the onset of this devastating disease and its complications. These are major multi-institution and multi-year efforts, as part of an overall $24 million clinical trials program in diabetes. In addition to these two major diabetes trials, some 24 smaller clinical trials on diabetes are also in progress, contributing necessary data with respect to treatment strategies and specific population groups in which prevalence is relatively high.

Our Division of Kidney and Urologic and Hematologic Diseases has large and highly significant clinical trials under way in several areas, including treatment of benign prostatic hyperplasia, or BPH, and alleviation of the morbidity and reduction of mortality associated with hemodialysis (a major cost to Medicare and other health care programs), and approaches to the problem of kidney disease and hypertension in African Americans (a population group at high risk of morbidity and mortality). These last two trials are the largest of the ones in progress in that Division, now that the major Modification of Diet in Renal Disease (MDRD) trial is complete, except for follow-up data analyses and further dissemination of findings. These and other clinical trials in the Division amounted to an investment of approximately $14 million in Fiscal Year 1994.

At the level of the 1996 President's Budget request, the NIDDK would be funding about $58,100,000 in clinical trials. This would provide for 62 trials, of which 52 are continuing and 10 are new.

Mr. Stokes: Are we doing better at getting the results of clinical trials disseminated expeditiously? In your Institute, is there a specific system in place for disseminating such information? Explain.

Dr. Gorden: The traditional mission of NIDDK has been and continues to be the conduct of basic and clinical biomedical research. Complementing this primary mission have been the information dissemination efforts of our three statutory national information clearinghouses in diabetes, digestive diseases, and kidney/urologic diseases. For example, information dissemination in diabetes has included research updates for physicians and access to an information database for health professionals and the public. Recently, this focus has expanded to include outreach programs for diabetes and for the prevention of obesity. These programs are conducted in cooperation with other NIH institutes and with the goals of Healthy People 2000 in mind. The national attention given to the findings of the major clinical trial, the Diabetes Control and Complications Trial, is a prime example of this new focus, as is the formation of our National Task Force on the Prevention and Treatment of Obesity. The Task Force evaluates the evidence from clinical trials and other research and disseminates appropriate findings and recommendations to physicians and the public. Obesity is, of course, a major risk factor in non-insulin-dependent (Type 2) diabetes and has growing clinical and economic impacts.

AIDS RESEARCH

Mr. Stokes: What is the most significant AIDS research that is underway at your institute? To what extent has knowledge gained in AIDS research and breast cancer research had positive spin-offs for advancing knowledge in other research emphasis areas under the purview of your institute?

Dr. Gorden: Major areas of ongoing AIDS research conducted or supported by the NIDDK have as their goals to determine the structures and functions of key HIV and immune system proteins; to understand and treat the wasting of AIDS; to develop novel AIDS therapies through immune reconstitution of the bone marrow; and to understand and prevent transmission of HIV via the semen. A significant advance in HIV research this past year was made by NIDDK intramural scientists. They determined the three-dimensional structure of the key component of HIV integrase, an enzyme that is responsible for splicing HIV DNA into the human genome. The structure of this enzyme provides the groundwork for the design of drugs to inhibit integrase action and thus block replication of the virus. Drug development will also be aided by the availability of an in vitro screening assay for HIV integration, developed previously at the NIDDK.

A number of studies we support related to AIDS have important implications for other diseases within the mission of the NIDDK. For example, insights into the pathogenesis and therapy of wasting in AIDS are relevant to other chronic diseases. In particular there are parallels between wasting in AIDS and in cystic fibrosis, since both conditions are characterized by chronic infection and often by malabsorption. Progress in understanding the altered metabolic patterns in AIDS should contribute to the general understanding of fat metabolism, which could also advance research on obesity. Findings from breast cancer research have direct relevance to uncontrolled growth in other hormone-responsive organs, such as the prostate and thyroid glands. In addition, the discovery of how steroids and growth factors interact in breast cancer provides an important model for potential therapies for osteoporosis.

RESEARCH PROJECT GRANTS

Mr. Stokes: The total number of research project grants funded by the NIH appears to be remaining fairly constant, around 24,000. According to the Congressional Justification, the NIH's FY 1996 budget would support a success rate of 23 percent. For your institute, to what extent has the success rate remained relatively flat over the past five years, explain.

Dr. Gorden: The NIDDK's success rate has varied considerably over the five years of 1992 to 1996. In 1992 the institute was able to fund 33 percent of all eligible research project grant applications. In 1993 that rate dropped to 22 percent. In both 1994 it rose to 25 percent and is estimated to remain at approximately that level in the current year, 1995. The estimated success rate for 1996, at the level of funding in the President's Budget request, is 18 percent. Two comparatively good years in a row will result in higher than normal noncompeting commitments in 1996, causing a relative shortage in competing funds, although the overall research project grant program will remain strong.

Mr. Stokes: What has been the trend in the average cost of research project grants over that same time period? What is the trend in terms of constant dollars?

Dr. Gorden: Over the five year period of 1992 through 1996, the average cost of research project grants has risen from $213,511 to $242,994. In constant dollar terms, after removing the effect of biomedical research inflation, the average has actually dropped slightly, from $213,511 in 1992 to $208,579 in 1996.

Mr. Stokes: What is the success rate for research applications received from minority researchers? From women? From African Americans? From Historically Black Colleges and Universities (HBCUs)?

Dr. Gorden: The following table illustrates success rates in 1994 according to the self-designated ethnic and gender identifiers which were included on about 95 percent of the applications that year.

Competing Grant Success Rates For Applicants by Ethnic Origin and Gender

NIDDK, Fiscal Year 1994

Asian	African-American	Hispanic	Native American	Unknown	White
20.3%	35.5%	8.5%	0%	31.3%	23.8%

Female	Male	HBCUs
19.9%	26.3%	0%

Mr. Stokes: For the same period, in real and in constant dollars, what has been the average cost of research project grants awarded to women? To minority researchers? To African American researchers? To Historically Black Colleges and Universities (HBCUs)?

Dr. Gorden: Actual figures on applications received by type of applicant are available through the 1994 actual year. Therefore the figures below address the five year period of 1990 through 1994. The HBCU figures below do not include HBCU participation in research training grants and clinical trials, both of which are significant.

Competing Grant Average Costs
For Applicants by Ethnic Origin and Gender
In Current and Constant Dollars

NIDDK, Fiscal Years 1990 - 1994
(Dollars in thousands)

	1990		1994	
	Current	Constant	Current	Constant
Women	140,483	140,483	175,512	149,245
Men	207,033	207,033	223,445	190,004
Gender Unknown	169,960	169,960	245,246	208,543
Asian	200,128	200,128	177,844	151,228
African American	109,979	109,979	161,256	137,122
Hispanic	169,491	169,491	360,028	306,146
Native American	186,210	186,210	---	---
White	198,676	198,676	220,632	187,612
Ethnicity Unknown	172,887	172,887	219,819	186,921
HBCUs	---	---	---	---

DIABETES

Mr. Hoyer: Last month, the Capitol Summit on Diabetes Research distributed a paper titled "Diabetes Research: A National Opportunity," which laid out a "blueprint for curing diabetes." The plan calls for Congress to appropriate $315 million for diabetes research, with $155 million for the Diabetes Division of NIDDK and $160 million for other NIH institutes. Are you familiar with this proposal? What progress might be made in curing diabetes if the recommendations of this paper were adopted?

Dr. Gorden: Yes, Mr. Hoyer, I am familiar with this document, which reflects the consensus of numerous scientific leaders in the diabetes community. The plan recommends an increase of $315 million for diabetes research through the NIH. This recommendation is for funding in addition to the $313 million that we estimate will be spent on diabetes research by the various institutes in FY 1996. Thus, the level of additional funding recommended would double the trans-NIH diabetes research effort, and include a near doubling of the NIDDK diabetes budget. Clearly, this would have an enormous positive impact on the pace of this research, on our understanding of processes that lead to diabetes, and ultimately on our ability to prevent, treat, and possibly cure diabetes. In this regard, the field of diabetes research is ripe with scientific opportunities. For example, in addition to the major clinical trials we are supporting to prevent diabetes, our Diabetes Prevention and Treatment Initiative includes programs to expand research on beta cell replacement therapies, on approaches to achieving euglycemia in diabetes, on the epidemiology of diabetes intervention and complications, and on diabetes prevention studies in minority populations.

Other diabetes initiatives that could be explored or expanded include: the genetics of diabetes, metabolic staging of non-insulin-dependent diabetes mellitus, the *National Diabetes Outreach Program*, kidney disease of diabetes mellitus, obesity and diabetes, and, of course, an expanded emphasis on basic, fundamental research on diabetes.

DUODENAL ULCERS

Mr. Hoyer: Dr. Gorden, you refer in your statement to the remarkable discovery that duodenal ulcers are caused by the bacterium *H. pylori*, and that this painful and costly condition can be cured easily and inexpensively with antibiotics. You also state that you will be exploring a possible link between *H. pylori* and stomach cancer. Other researchers are now investigating a vaccine against *H. pylori*. Would you please describe your plans for research in this area, and the prospects for its progress against both ulcers and cancer?

Dr. Gorden: Last year the Senate requested that the NIDDK assume a leadership role in developing a strategic plan to implement the research effort outlined at a recent Consensus Development Conference on *Helicobacter pylori in Peptic Ulcer Disease*, and to consult with the NCI, NIAID, and NICHD on aspects of the plan. The conference panel concluded that fundamental questions remain regarding the mechanisms by which *H. pylori* infection leads to gastrointestinal disease. Further research is critical to developing a better understanding of the natural history of this infection and to defining more precisely the subset of infected patients who will develop gastric cancer. Other unanswered questions relate to the role of *H. pylori* in a gastrointestinal disorder known as non-ulcer dyspepsia. Finally, clinical research is needed to pursue optimal treatment approaches to ulcer complications. The research agenda that is planned would address all these issues.

Research solicitations will be designed to promote basic research studies into such areas as bacterial genetics, virulence, and immune factors and antibiotic resistance associated with *H. pylori* infection. The plan also seeks to encourage clinical investigations into mechanisms leading to gastritis, dyspepsia, and gastric and peptic ulcer disease. In addition, proposals for clinical trials on functional dyspepsia and other *H. pylori* syndromes will be invited. The NCI and the NIDDK have already issued a research solicitation to encourage basic and clinical studies on *H. pylori* and human cancer. Other initiatives will prompt investigations into the natural history and pathogenesis of *H. pylori*, as well as vaccine development and enhanced epidemiology studies. Another clinical priority that will be addressed is the issue of how to treat most effectively and to prevent recurrent *H. pylori*-positive bleeding ulcers. The strategic plan offers much cause for optimism. To assess the plan and thus ensure its progress, an ad hoc advisory group will be reconvened every two to three years.

FIAU

Mr. Hoyer: Dr. Gorden, I know that the investigators at the NIDDK, and indeed, at the NIH were shaken and saddened by the deaths that resulted from the study of FIAU. You have referred briefly to the NIH's response to this tragedy. Could you outline in greater detail the specific changes which have been made at the NIDDK and the NIH in response to this study and the deaths which resulted from it.

Dr. Gorden: The FIAU study was indeed a tragedy felt deeply by the clinical research community throughout the country. As you know, this study has been scrutinized repeatedly by internal and external review bodies. These groups noted that exceptionally high standards of ethical conduct and medical practices were followed throughout the studies and that future risks inherent in clinical research in all likelihood cannot be completely eliminated by changes in research policies and procedures. Nonetheless, the FIAU experience has prompted all of us at the NIH to redouble our efforts to ensure the highest standards for review and conduct of clinical investigation aimed at minimizing the risks of clinical research.

The following are several changes in our clinical research policies and procedures which have been instituted since the tragic problems with FIAU:

- Non-clinical research is continuing within NIDDK and other NIH laboratories on the mechanisms of the toxicities of FIAU (and closely related anti-viral compounds).

- The NIH Office of Education and the Associate Director for Clinical Research have initiated a formal core curriculum for trainees in clinical investigation; the subjects include design and conduct of clinical trials, ethical obligations to patient volunteers, and legal and regulatory obligations to drug sponsors and the Food and Drug Administration.

- Investigators are being asked to address in the prospective design of *all* research protocols their plans for follow-up of patient volunteers, as was done in the FIAU study (i.e., at least for several months after completion of clinical trials in order to evaluate potential delayed effects of drug treatments).

- New policies have been developed for protocols submitted for IRB review to include expanded documentation (from the Clinical Investigators Brochure) of the results of pre-clinical pharmacological and toxicology testing of experimental drugs.

- IRBs are requesting (where appropriate) expanded use of independent data and safety monitoring committees during the conduct of clinical trials.

- Additional policies for protection of patient volunteers have been developed requiring:

  a) *explicit* notation in research consent forms of a patient representative (ombudsman) who is independent of the research team and who will be a resource to the patient volunteer if he/she has any concerns about the conduct of the research study;

  b) that the source (e.g., pharmaceutical company) of an experimental drug is specified in the consent forms;

  c) that patient volunteers be *explicitly* informed that the drug company sponsor, as well as the FDA, will have access to their medical and research records;

  d) that consent forms *explicitly* state that determination of the **safety** (in addition to efficacy) is the purpose of testing an experimental drug, particularly for drugs sponsored under an IND process.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1996 Budget — Page No.

Organization chart.. 2

Appropriation language.. 3

Amounts available for obligation.................................. 5

Budget mechanism table.. 6

Summary of changes.. 8

Budget authority by object.. 10

Administrative costs.. 12

Significant items in House and Senate
Appropriations Committee Reports.................................. 13

Authorizing legislation... 17

Appropriation history... 18

Budget authority by activity... 19

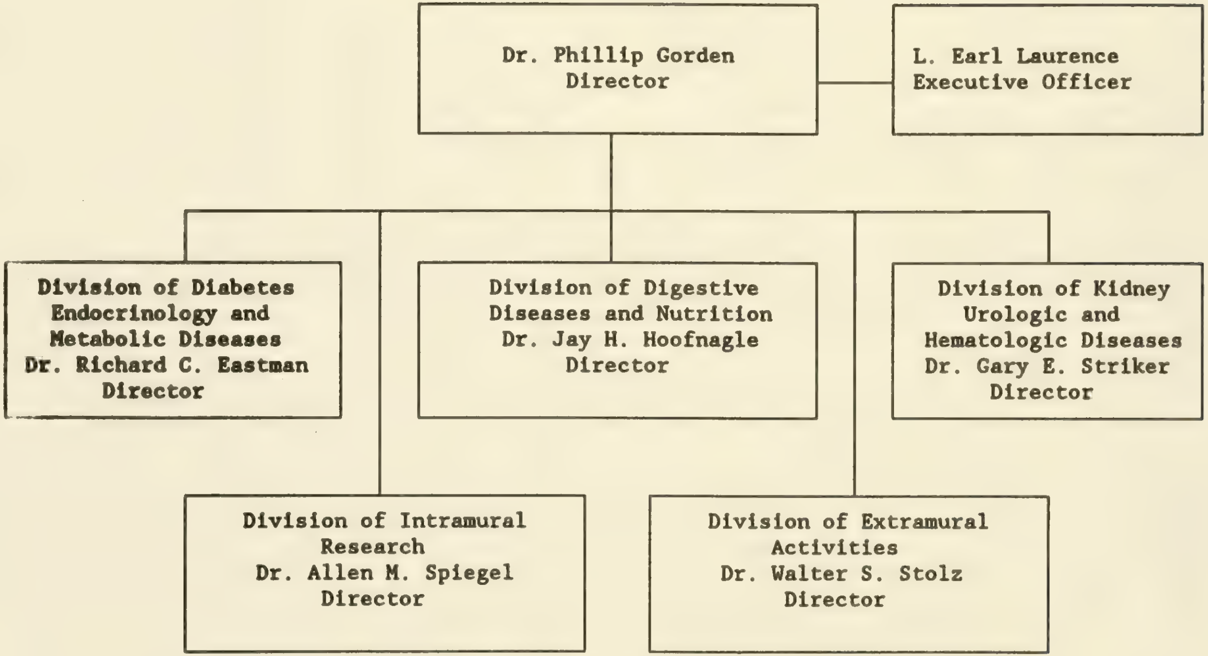
Justification:

- A. General statement... 21
- B. Extramural research... 24
- C. Intramural research... 39
- D. Research management and support......................... 42
- E. Detail of full-time equivalent employment (FTE)............. 44
- F. Detail of end-of-year employment............................ 45

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Organization Structure


Dr. Phillip Gorden
Director
L. Earl Laurence
Executive Officer
Division of Diabetes Endocrinology and Metabolic Diseases
Dr. Richard C. Eastman
Director
Division of Digestive Diseases and Nutrition
Dr. Jay H. Hoofnagle
Director
Division of Kidney Urologic and Hematologic Diseases
Dr. Gary E. Striker
Director
Division of Intramural Research
Dr. Allen M. Spiegel
Director
Division of Extramural Activities
Dr. Walter S. Stolz
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [$728,284,000] $748,798,000.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1995, P.L. 103-333.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

	1994 Actual	1995 Appropriation	1996 Estimate
Appropriation:	$716,054,000	$728,284,000	$748,798,000
Rescission in accordance with PL 103-211............			
Section 205 Procurement reduction................		-357,000	
Section 207 Rent reduction...		-6,000	
Section 513 S & E reduction..		-293,000	
Subtotal, adjusted Appropriation............	716,054,000	727,628,000	748,798,000
Comparative transfer to: Office of AIDS Research, NIH for HIV activities....	-10,437,000		
Comparative transfer to/from: Other NIH Institutes for Management Fund adjustment.	-1,841,000	-1,800,000	
Comparative transfer to/from: Office of the Director, NIH to NIDDK for the Division of Nutrition Research Coordination..............	+316,000	+446,000	
Subtotal, adjusted budget authority.................	704,092,000	726,274,000	748,798,000
Unobligated balance, lapsing...................	-432,000	---	---
Total, Obligations...........	703,660,000	726,274,000	748,798,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1994--$12,434,000; FY 1995--$13,000,000; 1996--13,500,000.

Also excludes funding for HIV activities: FY 1995--$10,752,000; FY 1996--$11,735,000, included in the Office of AIDS Research.

Note: Excludes $81,000 for Royalties in FY 1994 and $165,000 in FY 1995 for royalties.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism

	1994 Actual		1995 Appropriation		1996 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting........................	1,572	$340,250,000	1,558	$359,624,000	1,668	$412,877,000
Administrative supplementals..........	(136)	7,246,000	(41)	1,595,000	(41)	1,595,000
Competing	0	0	0	0	0	0
Renewal..........................	242	65,089,000	240	64,620,000	167	46,174,000
New..............................	340	61,152,000	336	60,732,000	228	43,266,000
Supplemental.....................	1	87,000	1	90,000	2	195,000
Subtotal, competing...........	583	126,328,000	577	125,442,000	397	89,635,000
Subtotal, RPGs................	2,155	473,824,000	2,135	486,661,000	2,065	504,107,000
SBIR/STTR.........................	58	7,938,000	56	10,681,000	57	11,322,000
Subtotal, RPG.................	2,213	481,762,000	2,191	497,342,000	2,122	515,429,000
Research Centers						
Specialized/Comprehensive centers.....	59	51,102,000	61	52,161,000	61	52,161,000
Other Research						
Research career programs..............	188	15,975,000	213	18,068,000	207	18,068,000
Cooperative clinical research.........	0	0	0	0	0	0
Minority biomedical research support..	0	1,757,000	0	1,794,000	0	1,794,000
Other research related...............	56	2,676,000	56	2,014,000	56	2,014,000
Subtotal, other research........	244	20,408,000	269	21,876,000	263	21,876,000
Total, research grants..................	2,516	553,272,000	2,521	571,379,000	2,446	589,466,000

Training						
Individual awards:						
Noncompeting	103	3,070,000	136	4,054,000	99	3,535,000
Competing	92	2,577,000	54	1,446,000	37	1,150,000
Subtotal, Individual	195	5,647,000	190	5,500,000	136	4,685,000
Institutional awards:						
Noncompeting	598	18,266,000	311	9,450,000	547	18,601,000
Competing	112	3,691,000	444	13,775,000	160	5,439,000
Subtotal, Institutional	710	21,957,000	755	23,225,000	707	24,040,000
Total, training	905	27,604,000	945	28,725,000	843	28,725,000
Research and development contracts	42	17,672,000	37	18,314,000	42	18,960,000
(SBIR/STTR)	(4)	(1,371,000)	(5)	(2,000,000)	(5)	(2,000,000)
	FTEs		FTEs		FTEs	
Intramural research	422	79,970,000	445	81,866,000	444	85,180,000
Research management and support	175	25,574,000	176	25,990,000	176	26,467,000
Total	597	704,092,000	621	726,274,000	620	748,798,000
Clinical Trials		(49,283,000)		(55,213,000)		(57,386,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1995 Estimated budget authority..............................	$726,274,000
1996 Estimated budget authority..............................	748,798,000
Net change..	+22,524,000

	1995 Current Estimate Base		Change from Base	
	(FTEs)	Budget Authority	(FTEs)	Budget Authority
Changes:				
A. Built-in:				
Intramural Research:				
1. One more day of pay..........		$37,476,000		+$142,000
2. January 1996 pay increase pay raise.................		37,476,000		+1,190,000
3. Annualization of January 1995 pay increase..........		37,476,000		+231,000
4. Within-grade increase........		37,476,000		+461,000
5. FECF........................		144,000		+5,000
6. Increased cost of centrally furnished services.......		21,476,000		+1,293,000
7. Increased cost of service and supply fund................		12,042,000		+371,000
8. Increased cost of supplies and materials............		10,383,000		+327,000
9. FTS.........................		345,000		-48,000
Subtotal............				3,972,000
Research Management and Support:				
1. One more day of pay..........		11,005,000		+42,000
2. January 1996 pay increase pay raise.................		11,005,000		+354,000
3. Annualization of January 1995 pay increase..........		11,005,000		+67,000
4. Within-grade increase........		11,005,000		+171,000
5. Working Capital Fund.........		635,000		-101,000
6. Increased cost of centrally furnished services.........		4,453,000		+430,000
7. Increased cost of service and supply fund..............		5,245,000		+152,000
8. Increased cost of supplies and materials............		4,652,000		+135,000
Subtotal............				+1,250,000

B. Program:	No.	Amount	No.	Amount
Increase:				
1. Research project grants				
a. Noncompeting	1,558	361,219,000	+110	+53,253,000
b. Competing	577	125,442,000	-180	-35,807,000
c. SBIR/STTR	56	10,681,000	+1	+641,000
Total	2,191	497,342,000	-69	+18,087,000
2. Research centers	61	52,161,000	---	---
3. Other research	269	21,876,000	-6	---
4. Training	945	28,725,000	-102	---
5. Research and development contracts	37	18,314,000	+5	+646,000
Subtotal				+18,733,000
Decrease:				
Intramural Research				
1. Decrease in administrative and FTEs			-1	-1,431,000
Subtotal				-1,431,000
Total changes				+22,524,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment........	621	620	-1
Full-time equivalent of overtime and holiday hours......................	3	4	1
Average ES salary..........................	106,264	109,664	+3,400
Average GM/GS grade........................	11.0	11.0	0
Average GM/GS salary.......................	46,802	48,300	+1,498
Average salary, grades est. by act of July 1, 1944 (42 USC 207)..............	76,687	79,141	+2,454
Average salary of ungraded positions........	22,780	23,509	+729
Personnel Compensation:			
Permanent Positions....................	$23,157,000	$24,139,000	+982,000
Positions other than permanent.........	9,175,000	9,667,000	+492,000
Other personnel compensation...........	1,620,000	1,688,000	+68,000
Special personnel service compensation..	6,338,000	6,650,000	+312,000
Subtotal, personnel compensation....	40,290,000	42,144,000	+1,854,000
Personnel benefits.........................	8,046,000	8,343,000	+297,000
Benefits for former personnel..............	145,000	150,000	+5,000
Total Personnel Compensation/Benefits.......	48,481,000	50,637,000	+2,156,000
Travel and transportation of persons........	1,100,000	1,300,000	+200,000
Transportation of things....................	175,000	180,000	+5,000
Rental Payments to Others...................	15,000	20,000	+5,000
Communications, Utilities & Misc............	2,210,000	2,230,000	+20,000
Total Communications, Utilities & Misc......	2,225,000	2,250,000	+25,000

Budget Authority by Object - cont'd

	FY 1995 Appropriation	FY 1996 Estimate	Increase or Decrease
Printing and Reproduction....................	550,000	575,000	+25,000
Consulting Services..........................	315,000	335,000	+20,000
Other Services...............................	5,164,000	3,820,000	-1,344,000
Purchase of Goods & Svcs. - R&D Mechanism....	4,500,000	4,700,000	+200,000
Purchase of Goods & Svcs. - P.E. Tap.........	3,672,000	3,800,000	+128,000
Purchase of Goods & Svcs. - MF SLUC..........		140,000	+140,000
Purchase of Goods & Svcs. - Other............	30,838,000	32,460,000	+1,622,000
Total Purchase of Goods & Svcs.	39,010,000	41,100,000	+2,090,000
R&D Contracts................................	13,814,000	14,260,000	+446,000
Total Contractual Services...................	58,303,000	59,515,000	+1,212,000
Supplies and Materials - Other...............	10,736,000	11,150,000	+414,000
Equipment....................................	4,600,000	5,000,000	+400,000
Grants, Subsidies and Contributions..........	600,104,000	618,191,000	+18,087,000
TOTAL..	726,274,000	748,798,000	+22,524,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Administrative Costs

	FY 1995 Current Estimate	FY 1996 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1).................	$23,157,000	$24,139,000	+$982,000
Other than full-time permanent (11.3).....	9,175,000	9,667,000	+492,000
Other personnel compensation (11.5).......	1,620,000	1,688,000	+68,000
Special personal services payments (11.8).	6,338,000	6,650,000	+312,000
Total, Personnel Compensation (11.9)......	40,290,000	42,144,000	+1,854,000
Personnel Benefits			
Civilian personnel benefits (12.1)........	8,046,000	8,343,000	+297,000
Benefits for former personnel (13.0)......	145,000	150,000	+5,000
Total Personnel Costs (11-13).............	48,481,000	50,637,000	+2,156,000
Travel (21.0)..............................	1,100,000	1,300,000	+200,000
Transportation of things (22.0)...........	175,000	180,000	+5,000
Rental Payments to others (23.2)..........	15,000	20,000	+5,000
Communications, utilities, and Miscellaneous Charges (23.3)...........	2,210,000	2,230,000	+20,000
Printing and reproduction (24.0)..........	550,000	575,000	+25,000
Consulting Services (25.1)................	315,000	335,000	+20,000
Other services (25.2).....................	5,164,000	3,820,000	-1,344,000
Purchases of Goods and Services from Govt. Accounts (25.3)...................	30,838,000	32,460,000	+1,622,000
Supplies and materials (26.0).............	10,736,000	11,150,000	+414,000
Total Administrative Costs................	99,584,000	102,707,000	+3,123,000

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item	Action Taken or to be Taken
1995 House Report	
Urological Diseases	
Institute to consider a further request for applications regarding the epidemiology of the disorder.	funded in FY 1995 and FY 1996 as a result of this RFA.
Digestive Diseases	
5. The House in its report 103-533, page 51, stated..."The Committee remains concerned about the digestive disease, celiac sprue syndrome, which involves severe reactions to certain food products. The Director should be prepared to discuss this serious problem at the 1996 budget hearings."	5. The Institute will continue to encourage research in celiac disease by publishing an RFA in FY 1995 entitled "Studies of Inflammatory Bowel Disease and Other Autoimmune Digestive Diseases."
1995 Senate Report	
Polycystic Kidney Disease	
1. The Senate in its report 103-733, page 79, stated..."The Committee is optimistic that the proposed new studies of the genetic molecular, and cellular events underlying PKD will provide a foundation for studies of other kidney diseases, and that the findings may be applicable to the other organs which are affected in PKD patients."	1. The NIDDK will continue to encourage basic research on the genetic, molecular, and cellular events underlying PKD. To that end, the Institute has issued an RFA for the support of such research and anticipates funding 12 to 15 grants in FY 1995 as a result of that RFA.
Urological Diseases	
2. The Senate in its report 103-733, pages 80 and 81, stated... "The Committee is concerned about the prevalence and costs of kidney stone diseases and the	2. The NIDDK is continuing to develop plans to accelerate research in both of these areas. The Institute has funded a George M. O'Brien Kidney and

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item

1995 House Report

Polycystic Kidney Disease	Action Taken or to be Taken
1. The House in its report 103-553, page 50, stated..."The Committee is pleased to learn of the significant scientific momentum generated by NIH-funded investigators to identify the gene(s) causing PKD and to be engaged in isolating and cloning them. The Committee urges NIDDK to expand this effort. Furthermore, the Committee expects the Institute to intensify research to understand the mechanism underlying the disease process in PKD and to develop novel treatments to prevent progression of PKD to end-stage renal disease."	1. The NIDDK has issued an RFA for the support of basic research to understand the mechanisms underlying PKD. It is anticipated that 12 to 15 grants will be funded in FY 1995 as a result of this RFA.
Diabetes	
2. The House in its report 103-533, page 50, stated..."The Committee views the problem of diabetes as an especially high priority and urges NIDDK to redouble its efforts in this time of extraordinary research possibilities. The Committee is excited by the results of the NIDDK-supported Diabetes Control and Complications Trial. This ten-year study found that the complications of type I diabetes could be reduced by nearly 60 percent by tightly controlling blood sugar levels. The Committee is also encouraged by the Diabetes Prevention and Treatment Initiative, a multi-faceted initiative aimed at preventing type I and type II	2. The NIDDK's Diabetes Prevention and Treatment Initiative encompasses basic and applied research, clinical trials, and national multicenter clinical trials for both insulin-dependent (IDDM) and non-insulin dependent diabetes (NIDDM). The multicenter clinical trials for IDDM and NIDDM are expected to run 5 and 7 years respectively. The Institute's Diabetes Interdisciplinary Research Programs (DIRP) is a major initiative in the genetics and molecular biology of diabetes. It is anticipated that 2 to 3 DIRP program project grants will be funded by the NIDDK in FY 95. The NIDDK will attempt to further strengthen its diabetes

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item	
1995 House Report	
Diabetes	Action Taken or to be Taken
diabetes. The Committee believes that this research is very important and expects NIDDK to use the increased resources provided to expand activities in this area. The Committee also expects NIDDK to expand its current efforts to find the genetic defect which is likely to be responsible for certain forms of diabetes and which may be the basis for vulnerability in all diabetes cases."	genes research portfolio through investigator-initiated grants.
Bionutrition	
3. The House in its report 103-533, page 51, stated..."The Committee urges NIDDK to expand its efforts regarding the bionutrition initiative. The Committee would urge NIDDK to consider expanding the clinical component of its bionutrition program for 1995 and to focus on women's health issues.	3. An NIDDK-led trans-NIH bionutrition RFA issued in FY 1994 has been highly successfulin attracting applications, 35 of which propose studies involving human subjects. A number of the applications also relate specifically to women's health issues, such as breast cancer, breastfeeding, uterine tissue integrity, fetal development, and bone growth. NIDDK also will be encouraging clinical nutrition research in anorexia and in the genetics of human obesity and diabetes.
Urological Diseases	
4. The House in its report 103-533, page 51, stated..."The Committee is pleased with the 1994 request for applications regarding clinical research on interstitial cystitis. The Committee encourages the	4. The NIDDK will issue in FY 1995 an RFA for basic research on bladder function and causes of interstitial cystitis, as well as epidemiologic studies. It is anticipated that approximately five or six new grants will be

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item

1995 Senate Report

Urological Diseases	Action Taken or to be Taken
impact of the urological complications of diabetes mellitus. Accordingly, the Committee encourages the NIDDK to develop plans for accelerating research in these areas of concern."	Urological Research Center that focuses on the pathogenesis and treatment of kidney stones, and applications for individual grants to study kidney stones have received priority funding. In FY 1995, the NIDDK is co-sponsoring a conference on the urological complications of diabetes mellitus to provide an opportunity for basic science and clinical investigators to determine the state of knowledge in this area and where future research should be directed.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1995 Amount Authorized	1995 Appropriation	1996 Amount Authorized	1996 Budget Request
Research and Investigation............	Section 301	42§241	Indefinite		Indefinite	
				>$697,549,000		>$720,073,000
National Institute of Diabetes and Digestive and Kidney Diseases......	Title IV, Part C	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards..................	Section 487(D)	42§288	Such sums as necessary	$28,725,000	Such sums as necessary	$28,725,000
Total Budget Authority...				$726,274,000		$748,798,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Apppropriation 1/
1987	$418,971,000	$515,455,000	$502,628,000	$511,124,000
1988	440,504,000	563,768,000 2/	549,784,000	534,733,000
1989	562,258,000 3/	546,902,000 4/	565,908,000	559,538,000
1990	577,235,000 5/	590,276,000	593,497,000	589,594,000 6/
1990 Sequester				-8,117,000
1991	605,349,000	613,686,000 7/	626,986,000	615,272,000 8/
1991 Sequester				-8,000
1992	658,557,000	667,820,000	652,861,000	659,538,000 9/
1993	699,809,000	688,633,000	688,633,000	681,342,000 10/
1994	677,135,000	716,054,000	716,054,000	716,054,000
1995 11/	731,500,000	726,784,000	728,784,000	727,628,000 12/
1996 11/	748,798,000			

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions.

2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

3/ The 1989 Request excludes funds for AIDS research and education ($3,650,000) that has been proposed for consolidation at the Office of the Assistant Secretary for Health.

4/ Excludes $25,509,000 in NRSA training programs not considered.

5/ The 1990 Request excludes funds for National HIV program ($5,394,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of $2,293,000.

7/ Excludes $23,872,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of $15,238,000 and $1,762,000.

9/ Excludes enacted administrative reductions of $435,000 and $4,107,000.

10/ Excludes enacted administrative reductions of $7,291,000.

11/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research.

12/ Excludes enacted administrative reductions of $357,000, $6,000, and $293,000.

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(Dollars in thousands)

	1992 Actual		1993 Actual		1994 Actual		1995 Appropriation		1996 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Diabetes, Endocrinology and Metabolism.......		$274,326		$275,865		$294,591		$302,934		$312,137		+9,203
Digestive Diseases and Nutrition............		128,606		137,959		139,947		144,634		149,029		+4,395
Kidney disease, urology and hematology.......		147,282		153,743		163,677		170,850		175,985		+5,135
Subtotal, Extramural.....		550,214		567,567		598,215		618,418		637,151		+18,733
Intramural Research......	457	79,592	453	82,449	422	79,970	445	81,866	444	85,180	-1	+3,314
Research management and support............	172	24,468	170	24,052	175	25,475	176	25,990	176	26,467	---	+477
Subtotal obligations.	629	654,274	623	674,068	597	703,660	621	726,274	620	748,798	-1	+22,524
Unobligated Balance Lapsing..............		619		158		432		---		---		
Total, Budget Authority..	629	654,893	623	674,226	597	704,092	621	726,274	620	748,798	-1	+22,524

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
597	$704,092,000	621	$726,274,000	620	$748,798,000	-1	+$22,524,000

General Statement

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research related to many serious and costly diseases affecting the public health. These include but are not limited to: diabetes mellitus; endocrine diseases including osteoporosis; metabolic diseases including cystic fibrosis; digestive diseases including those of the liver and biliary tract, pancreas, and gastrointestinal tract; nutrition and eating disorders including obesity; kidney failure; genitourinary diseases; and diseases of the blood-forming organs. Several of these diseases are among the leading causes of disability and death; all seriously affect the quality of life of those who have them; and each year, their economic burden exceeds $300 billion.

The NIDDK's programs are closely linked by common fundamental biological questions. The Institute places a high priority on research that explores those questions, and on transferring the promising results of basic research to clinical research on preventing and treating disease. This year, NIDDK-supported basic research was recognized by the award of the 1994 Nobel Prize in Physiology or Medicine to Dr. Martin Rodbell for a discovery he made during his career in the Institute's intramural program. Rodbell identified the phenomenon by which signals are transmitted from outside to inside the cell through the binding of GTP to what are known as G proteins. Since the time of Rodbell's discovery, abnormalities in this type of cell communication have been associated with several widespread diseases, including diabetes, cancer, and cholera, as well as rarer diseases such as McCune-Albright syndrome and Albright's hereditary osteodystrophy.

NIDDK-supported researchers in both the extramural and intramural programs have made several key fundamental discoveries over the past year that hold similar promise of improving disease prevention and treatment in the future. Investigators have identified an obesity gene thought to be involved in regulating appetite. A gene that is overexpressed uniquely in the skeletal muscle of individuals with non-insulin-dependent diabetes mellitus (NIDDM) was identified and will be studied to determine whether it is responsible for the misregulation of glucose processing that leads to NIDDM. Further, growing evidence suggests that coxsackie virus may trigger insulin-dependent diabetes mellitus in genetically susceptible individuals. A gene for autosomal dominant polycystic kidney disease was also identified, culminating an intensive search set in motion by NIDDK grantees in 1985. A clue to the genetic basis of hypertension was provided by the discovery that a gene involved in the reabsorption of sodium in the kidney underlies Liddle's syndrome, an inherited form of high blood pressure. Researchers have cloned a cell surface receptor from the parathyroid cell that senses and responds to calcium levels in the body and sets in motion a series of events that result in the signalling of bone cells to increase calcium resorption. Progress is also being made in narrowing the search to identify the genes responsible for Wilson's disease and for hemochromatosis, inherited disorders of trace metal metabolism that can result in end-stage liver disease.

Although identification of disease genes is the first step toward the possibility of gene therapy, current techniques for gene therapy must be refined before they can be used widely to treat disease. Retroviruses, for example, have been used successfully to transfer healthy genes into human cells. However, they have the disadvantage of being able to infect all kinds of cells. The development this year of a way to alter retroviruses so that they can target specific cells could reduce the chance of a gene's being inserted inadvertently where it would cause harm. In another area, early studies of gene therapy for familial hypercholesterolemia have shown good results, and investigators are developing methods for storage of liver cells for use in gene therapy or transplantation procedures. Progress is also being made in developing gene therapy techniques for cystic fibrosis.

Structural biologists in the Institute's intramural program recently reported two major achievements. They have determined the structure of the catalytic core of HIV integrase, an enzyme responsible for splicing the DNA of the AIDS virus into the human genome, and the structure of a key part of the p53 protein, which is important in suppressing several common cancers. Knowledge about the structures of these proteins may provide a foundation on which to base the design of drugs to inhibit HIV replication or to suppress tumor growth.

The discovery of "thrombopoietin," a platelet regulatory factor, is expected to lead quickly to the development of a new therapy for platelet deficiencies, much as erythropoietin, which stimulates the production of red blood cells, is currently used to treat anemia. Erythropoietin is considered a highly successful biotechnology drug, with over $1 billion in sales worldwide. The discovery that administration of parathyroid hormone (PTH) prevents spinal bone loss in young women with endometriosis who are deficient in estrogen because of other hormone therapy has enormous clinical implications for a wider patient population. Researchers believe that PTH likely will prevent bone loss in women with estrogen deficiency from other causes.

The NIDDK currently sponsors several large Institute-initiated clinical trials, including trials to delay or prevent insulin-dependent or non-insulin-dependent diabetes mellitus, to delay progression of kidney disease associated with hypertension in African Americans, to reduce the morbidity and mortality of hemodialysis patients, and to assess medical therapy for benign prostatic hyperplasia. Another initiative focuses on diabetes interventions in seven minority populations that are disproportionately affected by the disease.

Two outreach programs were launched this year. With the slogan "Do Your Level Best," the Institute began the National Diabetes Outreach Program to disseminate the results of the Diabetes Control and Complications Trial. The Institute also has set up a Weight-Control Information Network (WIN) to develop effective methods of communicating weight control information to health professionals and the general public.

The President's appropriation request of $748,798,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Diabetes and Digestive and Kidney Diseases during the last five years has been as follows:

	Amount	FTE
FY 1991	$609,700,000	603
FY 1992	654,893,000	629
FY 1993	674,226,000	623
FY 1994	704,092,000	597
FY 1995	726,274,000	621

Purpose and Method of Operation

The major program areas of the Institute foster basic, clinical, and applied and developmental research through investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, research and development contracts, and intramural research. Training for research careers and/or teaching is accomplished through National Research Service Awards. Particular emphasis is placed on encouraging individuals from underrepresented minority populations to pursue careers in biomedical research. NIDDK-supported information clearinghouses distributed more than 400,000 documents last year to professionals, patients, and the public about the diseases within the Institute's mission.

Overall Budget Policy

The FY 1996 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases provides a 3.1% percent increase and totals $748,798,000, an increase of $22,524,000 over the FY 1995 level.

In FY 1996, the request will support 2,122 research project grants as compared to 2,191 in FY 1995. This reflects a total decrease of 69 RPGs and $18,087,000 as compared to FY 1995

The FY 1996 request includes funding for 61 research centers, 207 research career awards, 56 other research grants, 843 research trainees, and 42 R&D contracts, the same number as funded in FY 1995.

The FY 1996 requests for Intramural Research and Research Management and Support are net increases. Funding for the intramural program is $85,180,000, an increase of $3,314,000 over the FY 1995 level of $81,866,000. Funding for research management and support is $26,467,000, an increase of $477,000 over the FY 1995 appropriation of $25,990,000. They provide for built-in mandatory increases such as centrally furnished services and for annualization of the 1995 pay raises, offset by savings from administrative cost and staffing reductions (1 FTE).

24

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

Budget Authority:

FY 1994 Actual	FY 1995 Appropriation	1996 Estimate	Increase or Decrease
$598,548,000	$618,418,000	$637,151,000	+$18,733,000

Funding for the Extramural Program during the last five years has been as follows:

	Amount
FY 1991	$513,846,000
FY 1992	550,770,000
FY 1993	567,725,000
FY 1994	598,548,000
FY 1995	618,418,000

Rationale for Budget Request

The FY 1996 budget request for the Extramural Program is $637,151,000, an increase of 3.0 percent over the FY 1995 appropriation of $618,418,000. With the FY 1996 extramural request these funds will provide support for the following activities: Diabetes, Endocrinology, and Metabolic Diseases, $312,137,000, an increase of $9,203,000 or 3.0% over the FY 1995 estimate of $302,934,000; Digestive Diseases and Nutrition, $149,029,000, an increase of $4,395,000 or 3.0% over the FY 1995 estimate of $144,634,000; Kidney, Urologic, and Hematologic Diseases, $175,985,000, an increase of $5,135,000 or 3.0% over the FY 1995 estimate of $170,850,000.

Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK's Diabetes, Endocrinology, and Metabolic Diseases program has primary responsibility at the National Institutes of Health for extramural research and research training in endocrinology and metabolism, with special emphasis on diabetes, cystic fibrosis, and other diseases and disorders encompassed by these disciplines.

Diabetes

The NIDDK is the lead agency of the Federal government for research efforts to combat diabetes mellitus and its complications. Diabetes is the sixth leading cause of death from disease in the U.S., afflicting an estimated 13 to 14 million people, but approximately one-half of these cases are undiagnosed. It is also the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for stroke, heart attack, and premature death. The annual economic cost to the nation of diabetes is estimated to be nearly $92 billion. In addition, minority populations, including African Americans, Hispanics, Native Americans, Hawaiians, and Alaska Natives, are disproportionately affected by diabetes and subsequently by its enormous cost burden.

Insulin-Dependent Diabetes Mellitus (IDDM): Approximately 500,000 to 750,000 Americans have IDDM. Most of these people are children or young adults. IDDM occurs when a person's immune system mistakenly attacks and destroys the insulin-producing beta cells of the pancreas. Eventually, these individuals require insulin from an external source in order to regulate their blood glucose level and thus survive.

Results announced last year of the NIDDK's landmark Diabetes Control and Complications Trial showed that very careful management of blood glucose levels dramatically reduces the risk of life-threatening microvascular complications -- eye, kidney, and nerve damage -- due to diabetes. Following release of the DCCT results, it was apparent that these findings could have profound implications for the life-long health, and quality of life, for insulin-dependent diabetics. Thus, the NIDDK has initiated efforts designed to disseminate, evaluate, and investigate these results. Early in FY 1995, for example, the Institute launched the National Diabetes Outreach Program to help disseminate the results of the DCCT to patients, health care professionals, and the general public regarding the importance of controlling blood sugar levels. The Institute's Division of Diabetes, Endocrinology and Metabolic Diseases and National Diabetes Information Clearinghouse are collaborating with voluntary health organizations, the private sector, and with other federal agencies to address the issues surrounding dissemination of the DCCT results to the diabetes community and to people at risk for developing IDDM.

NIDDK-supported research has uncovered evidence that an environmental factor is involved in the initiation of IDDM. Thus far, however, researchers have not been able to identify this initiator of IDDM. Recent studies suggest that a virus may trigger the onset of IDDM. In examining two patients who had died within a few weeks after developing their diabetes, investigators found that pancreatic infections had occurred, and that a "superantigen" from an infectious agent had triggered an overwhelming immune response -- one much greater than would otherwise be necessary to subdue the infection. All known superantigens are products of either bacteria or viruses; though in this case a virus is strongly suspected.

Subsequent to this report, two other research teams published findings that implicate coxsackie viruses as the IDDM trigger. One team found that these viruses initiate IDDM in genetically susceptible mice, while the other group demonstrated that the autoimmune reaction to destroy pancreatic beta cells is triggered by a close similarity between a coxsackie virus protein and a protein found in the pancreas. Some researchers believe a strong case is building that coxsackie viruses are the key triggering agent. If this turns out to be the case, a vaccine may be developed to immunize susceptible individuals against IDDM.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM): NIDDM accounts for about 90 percent of all diabetes. What makes NIDDM so insidious is that it often is diagnosed only after it has wrought years of damage on the heart, blood vessels, kidneys, eyes, and nerves. In addition, as NIDDM develops it becomes increasingly difficult to treat. Therefore, if NIDDM can be prevented, or even significantly delayed, the health and economic implications will be significant.

There is growing belief that NIDDM, which generally appears in middle age, is in fact a preventable disease. Several studies have demonstrated the protective effects of regular exercise and healthful eating in people at risk for NIDDM. It has also been shown that a drug, called troglitazone, reduces elevated blood glucose and insulin concentrations in diabetic animals and humans. Now, a recent NIDDK-supported study has shown that troglitazone improves the two conditions that give rise to NIDDM -- impaired glucose tolerance and insulin resistance -- and hypertension in obese, but not yet diabetic, individuals. These abnormalities are risk factors for the development of cardiovascular disease. Thus, troglitazone may be of potential benefit in preventing NIDDM and may improve the risk profile for the development of cardiovascular disease.

Successful treatments for NIDDM can only come from a comprehensive understanding of the process that leads to the disease. Thus, the NIDDK continues to be very supportive of research on the genetic, metabolic, and environmental risk factors that result in NIDDM. As one example, NIDDK grantees now have identified the molecular defect that causes insulin resistance in animals. Insulin resistance is one of the key features of NIDDM. Other defects in the insulin response pathways have been determined, and this new knowledge is quickly being applied to a better understanding of the insulin resistance observed in NIDDM. Identifying the sites of metabolic abnormality should lead to a more precise diagnosis of NIDDM, a basis for rational therapy, and improved ability to examine the role and timing of environmental factors -- such as obesity -- as precipitating events for the overt diabetic condition.

To evaluate the risks and benefits of intensive management for NIDDM, the NIDDK recently cosponsored an international scientific conference. Several ways of managing NIDDM to achieve normal or near-normal blood glucose levels were discussed. The proceedings of the conference will be published later this year.

Diabetes Prevention and Treatment Initiative (DPTI): To investigate methods of preventing and treating diabetes, the NIDDK has begun a new, comprehensive initiative targeted at preventing diabetes and its complications. The DPTI encompasses basic and applied research, clinical trials, and national multicenter clinical trials. New strategies for the prevention of diabetes will encompass ethnically diverse and multi-racial patient populations. A major element of the DPTI is the IDDM Prevention Trial, a national multicenter clinical trial for the prevention of IDDM. The trial will investigate whether intervention prior to clinical onset of IDDM can delay the disease in first-degree relatives of individuals with established IDDM. At-risk individuals will be treated either with low dose insulin injections or with oral insulin administration. Because IDDM is considered an autoimmune disease, these approaches are anticipated to "immunize" the at-risk individuals against self-destruction of their insulin-secreting pancreas cells. This trial is expected to run five years.

The second major element of the DPTI is a clinical trial of intervention strategies to prevent the onset of NIDDM in people with impaired glucose tolerance or gestational diabetes mellitus who are at high risk for developing the disease. NIDDM disproportionately impacts minority populations, who accordingly will be overrepresented among the trial participants in order to ensure applicability of the results to these groups. Lifestyle and pharmacologic interventions are being evaluated for inclusion in this study. The trial is a collaborative effort between the NIDDK, the National Institute of Child Health and Human Development and the NIH Office of Research on Minority Health, and is scheduled to last seven years.

Genetics of Diabetes: Genetics appears to be the common denominator underlying the various factors that lead to diabetes. Intensified genetics research offers great promise for understanding, controlling, and preventing diabetes. The NIDDK continues to enhance support for both the basic understanding of diabetes and for the direct application of this knowledge to the clinic.

Institute-supported research on diabetes includes a major initiative to encourage research on the genetics of diabetes and the search for diabetes genes. Both forms of diabetes mellitus are believed to be determined at least in part by genetic makeup, and multiple genes are thought to be involved. Further, while IDDM and NIDDM patients may have the same clinical manifestations, these characteristics may be caused by alterations in a number of completely different genes. This also is true for the various subtypes of NIDDM. Many genes associated with NIDDM have been isolated but, in the aggregate, these genes account for no more than a few percent of NIDDM patients. The genes or genes responsible for the most common type or types on NIDDM have not yet been uncovered. Recently, however, NIDDK grantees discovered a gene whose overexpression is unique to the skeletal muscle tissue of individuals with NIDDM. Skeletal muscle is the major site of insulin resistance in the diabetic and pre-diabetic patient. Expression of the *Rad* gene, which is part of the *Ras* gene family, was increased nearly 9-fold in diabetics compared with non-diabetics. Proteins related to *Ras* have been implicated in insulin action, and there is evidence that members of the *Rab* family may be involved in glucose transport in response to insulin. Thus, overexpression of *Rad* may be responsible for the aberrant regulation of glucose processing that gives rise to NIDDM. The precise role of *Rad* in NIDDM is being explored.

Of the genetic factors or genes involved in determining susceptibility to IDDM, only certain variations of specific immune response genes have been shown to correlate with susceptibility to IDDM. These genes, located in humans on chromosome 6 in the region of the human leukocyte antigen (HLA), and in the insulin gene region on chromosome 11, confer protection from, and susceptibility to, IDDM. NIDDK grantees have made major contributions in identifying these genes. There is new evidence that a third gene area (a second region of chromosome 11) may be a determining factor for IDDM. It therefore appears that there are several minor, but no major, contributing genes for IDDM. Scientists continue to investigate the role of known genetic factors in the development of IDDM, and search for new ones, with the hope that new knowledge will lead to effective therapeutic and preventive strategies for this disease.

Diabetes in Minority Populations: Research has shown that the most prominent risk factors for NIDDM are a family history of diabetes, obesity, insulin resistance, hyperinsulinemia, a history of gestational diabetes, and impaired glucose tolerance. African-Americans, Hispanic-Americans, and Native Americans are disproportionately affected. The U.S. Congress and the Department of Health and Human Services have highlighted the growing problem of diabetes in minority populations as important public health issues deserving increased research effort.

As part of its continuing commitment to address this need, the NIDDK recently initiated a major clinical trial of preventive intervention strategies targeted at individuals with impaired glucose tolerance, a history of gestational diabetes, and/or newly diagnosed NIDDM. Minorities will make up 50 percent of the study population. Interventions may include diet, exercise, and pharmacologic agents. This new initiative is a collaboration between the NIDDK, the NIH Office of Research on Minority Health, and the National Institute of Child Health and Human Development. Another component of the NIDDK's diabetes prevention effort in minority populations is the Institute's program initiative entitled "Intervention Studies in Diabetes Among Minority Populations," which will broaden understanding of the cause, course, diagnosis, treatment, cure, and prevention of NIDDM and its complications among African, Asian, Hispanic, and Native Americans, as well as Alaska Natives, Pacific Islanders and Native Hawaiians.

In addition, the NIDDK and the NIH Office of Research on Minority Health are collaborating on a clinical study of the development of NIDDM in Mexican-American Women. The aim of the study is to identify early metabolic defects in Mexican-American women who are at high risk for NIDDM because of prior NIDDM associated with pregnancy. In future studies, these early defects may be targeted for interventions aimed at delaying or preventing the onset of NIDDM.

Endocrinology

Osteoporosis and Related Bone Disorders: As a major participant in osteoporosis and related bone disorders research at the NIH, the NIDDK continues to strongly encourage and support investigations that are vital to the health of America's aged population. This past year, the Institute supported a major research advance related to parathyroid hormone (PTH), which is the key hormone regulating the transfer of calcium from the blood into bone. It had long been known that the amount of circulating calcium, a key mineral component of bone, had a role in regulating the amount of PTH secreted by the parathyroid gland. However, the precise mechanism by which this endocrine organ was able to sense and respond to calcium was unknown. In a major and far-reaching advance, NIDDK investigators have identified, cloned, and sequenced a cell surface receptor from the parathyroid cell which carries out this function. This calcium receptor serves to "sense" extracellular levels of calcium and signal the parathyroid cell to regulate levels of secretion of PTH. Thus, when extracellular calcium levels are low the parathyroid calcium receptor triggers PTH release which, in turn, signals bone cells to increase the resorption of calcium from bone. This receptor belongs to a new class of the cell surface receptors which serve to signal a vast variety of cellular functions throughout the body. This basic research finding has almost immediately been translated into a major advance in the understanding of human disease.

The menopause, particularly at an early age, with its resultant decrease in estrogen levels, places women at increased risk for osteoporosis and resulting bone fractures. After many years of research on fundamental aspects of hormones and bone metabolism, NIDDK-supported researchers have reported major progress in possibly preventing osteoporosis. They demonstrated that intermittent administration of PTH reverses spinal bone loss in young women with endometriosis who are deficient in estrogen due to other hormone therapy. This finding has enormous implications for menopausal women, particularly those who do not receive estrogen-replacement therapy. Researchers believe that PTH may also prevent bone loss in women with other causes of estrogen deficiency.

Hormones and Cancer: The ability of cells to multiply by cell division is essential to the vitality of many organs and tissues. However, uncontrolled cell division can lead to inappropriate tissue growth and cancer. The ability of cells to regularly undergo cell division involves a complex series of events mediated by the expression, often in a hormone-dependent fashion, of key proteins which regulate whether the cell remains in a quiescent stage or progresses through the cell cycle to cell division. One such protein, call PRAD1 or cyclin D1, was known to be involved in the initiation of benign growth. Investigators have now shown that the overexpression of PRAD1/cyclin D1 in transgenic mice causes lesions in breast tissue that go on to become breast cancer. The protein thus appears to disrupt normal growth regulation in breast tissue sufficient to cause tumors to form.

Evidence has also emerged that another cell cycle regulatory protein, the retinoblastoma protein (RB) is missing in parathyroid cells that have become malignant. While alterations in cyclin D1 result in benign hyperplasia, the complete inactivation of the RB gene may signal the next stage in the transformation of benign hyperplasia to malignant carcinoma. Only with further understanding of these basic mechanisms of cancer can potential diagnostic and therapeutic approaches be designed to combat abnormal cell growth.

Metabolic Diseases

Cystic Fibrosis (CF): As the lead Institute for CF research at the NIH, the NIDDK continues its commitment to foster progress in combating this devastating disease of children and young adults. In 1993 and 1994 the Institute funded the first three NIH research centers for gene therapy of cystic fibrosis and other genetic diseases. As a result of this effort, investigators have identified specific types of cells in the lung as potential targets for correction by gene therapy, and have been able to correct the lethal CF-induced intestinal abnormalities in an animal model for CF. Other NIDDK-supported investigators are solving problems related to the use of viruses as carriers for gene therapy, including development of new methods of introducing genes to the host site, and have achieved stable correction of genetic deficits with an adeno-associated virus carrier. While many barriers still must be overcome, these and other promising advances are moving researchers closer to a cure for CF.

30

CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane regulator (CFTR). A major barrier to determining the mechanism by which mutations in CFTR cause disease has been the difficulty in expressing and purifying sufficient quantities of CFTR for characterization of the three dimensional structure of the normal and mutant proteins. Investigators instead are now studying functionally important segments of CFTR, have isolated some, and are developing methods to crystallize these partial proteins in order to determine their three-dimensional structure. This work suggests a possible alternate approach to gene therapy in which a small, stable protein designed to interact with a specific functional cite on mutant CFTR might restore CFTR to the normal state.

Digestive Diseases and Nutrition

Digestive Diseases

Disorders of the digestive tract are among the leading causes of hospitalization, surgery, and disability in the U.S. and incur tremendous social and economic consequences. Some twenty million Americans are treated for a chronic digestive disease each year, resulting in current costs of $50 billion a year in lost wages, reduced productivity, health care expenditures, and disability payments. NIDDK supports basic and clinical biomedical research on the normal function and diseases of the liver and biliary tract, pancreas, esophagus, stomach, small and large intestines, and anorectum.

Inflammatory Bowel Disease (IBD): The chronic inflammatory process that occurs in IBD results in tissue injury and destruction as a direct consequence of the effects of certain proteins known as cytokines and inflammatory mediators secreted by activated immune cells. Recent understanding of these immune responses has been clarified with development of the transgenic "knockout" mouse. NIDDK grantees have begun investigations of a mouse model of IBD which has undergone specific genetic alterations rendering these mice incapable of producing cytokines, and eliminated particular types of T cell receptors which relate to disorders of immunoregulation. Because current drug treatments have been targeted to the immune system as well as the destructive inflammatory processes, these "knockout" mice should provide an excellent model to understand drug mechanisms. In this regard, researchers have recently shown that the antimicrobial metronidazole exerts its beneficial effects by interfering with the process by which white blood cells adhere to endothelial cells to promote inflammation and not solely by its antibacterial properties. These findings provide a better rationale for selecting this therapeutic agent in noninfectious forms of IBD. Future therapeutic options should include efforts to develop more specific inhibitors of this adhesion process. In addition, the "knockout" mouse should be a useful tool to demonstrate the mode of action of anti-inflammatory agents and other promising drugs.

Liver Diseases: NIDDK-supported investigators are narrowing their search to identify and clone the gene(s) responsible for Wilson's Disease and hemochromatosis, inherited disorders of trace metal metabolism that can result in end-stage liver disease. The Wilson's gene has been tracked to specific loci on chromosome 13, and a candidate gene has been isolated. The nature of the candidate gene is now being characterized. It is a transmembrane copper binding, ATPase protein probably responsible for correct trafficking of copper through the cell. In hemochromatosis, investigators are homing in on their search for the exact location of the gene, which is believed to reside near the HLA region on chromosome six. Advances associated with Crigler-Najjar syndromes type I and type II -- inherited disorders of efficient bilirubin excretion -- also have been recently reported. Molecular genetic studies have led to the cloning of the gene complex that encodes for human bilirubin and have identified gene mutations. These advances have immediate implications for possible gene therapy of these rare but fatal forms of liver disease. Identifying the gene(s) related to Wilson's disease, hemochromatosis and Crigler-Najjar syndromes will allow for familial genetic tests for individuals at risk. Early diagnosis of the diseases can then result in management of the disease pathology. Once the mutations have been characterized, gene therapy of these liver diseases can then be explored.

Liver-assist devices: Extracorporeal liver support in patients with acute liver failure represents a unique new resource for bridging the patient to transplantation. The procedure is performed at relatively low cost and can be used repetitively to improve a patient's chances for survival. Successful use of an extracorporeal liver device has now been demonstrated in a clinical setting. Liver-assist devices developed by NIDDK investigators are currently being evaluated in randomized controlled trials. Early results show impressive improvements in liver function tests in these critically ill patents. The major use of these devices will be to stabilize patients and keep them from developing irreversible brain and other organ damage while waiting for an available liver for transplantation. The extracorporeal liver device represents the first generation of an artificial liver, which is a critical need owing to the shortage of donor livers for transplantation. Modification of the techniques and device components will improve efficiency and promote maximum use and success in the second generation of the support system.

Gene therapy: In its early stages, liver-directed gene therapy is being targeted to liver metabolic diseases with the ultimate goal of extending it to other liver diseases and to replacing the costly procedure of liver transplantation. Following successful animal studies, a human liver gene therapy approach to correct familial hypercholesterolemia (FH) was developed. The recipient, a 29 year old woman was transplanted with her own liver cells, which were genetically corrected with recombinant retroviruses carrying the low density lipid (LDL) receptor, and tolerated the procedures well. The patient's LDL/HDL ratio declined from 10-13 before gene therapy to 5-8 following gene therapy, and improvements have been sustained for the duration of the treatment (18 months). This study represents a new and novel approach to liver disease which has moved from the laboratory bench to the bedside.

A ready supply of human liver cells will be necessary for liver cell transplantation and gene therapy to be used as a standard therapy. Because liver cells do not readily proliferate in cell culture, cryopreservation is critical for providing a single or multiple source of liver cells. Investigators recently reported the development of a freezing procedure for liver cells cultured in a sandwich configuration that enables them to maintain satisfactory levels of long-term viability after the freeze-thaw cycle. These data suggest that a standardized storage procedure for liver cells can be developed. Additional studies are needed to improve the efficiency of gene transfer and gene therapy.

Ulcers: Two long-held dictums "No acid, no ulcer" and "Once an ulcer, always an ulcer" have been disproved. It is now widely accepted that peptic ulcer disease is a consequence of the bacterium, *Helicobacter pylori*. Since 1982 when the association of *H. pylori* and duodenal ulcer disease was first noted, major strides toward understanding the bacteriology, pathophysiology and natural history of *H. pylori* infection in man have been made. Previously, conventional treatment for peptic ulcer disease included either antacids, histamine H_2 receptor blocking agents, or proton pump inhibitors. However, ulcer recurrence was always a major problem. The 1994 Consensus Development Conference on *Helicobacter pylori*, cosponsored by the NIH and NIDDK, concluded that *H. pylori*-positive ulcers should be treated with a two-week regimen of antimicrobial agents in addition to antisecretory agents. This new treatment regimen proposed by NIDDK grantees effectively eradicates the organism and prevents the recurrence of the disease. It is anticipated that this approach will alter the natural history of peptic ulcer disease as well as have major implications in reducing health care expenditures over time.

Nutrition

The NIDDK fosters and supports research in the broad areas of fundamental and clinical nutrition. Application of the most current techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to expand our knowledge of the function and requirements of nutrients, the relationship of diet and nutrients to health and disease, and the prevention and treatment of diseases as an outgrowth of nutrition research. Clinical problems of interest to the NIDDK include obesity, anorexia nervosa, diabetes, chronic renal disease, end-stage liver disease, gastrointestinal dysfunction, bone disease, total parenteral nutrition, and combined nutrient-drug interactions and management of patients.

Bionutrition: Historically, the NIDDK has been the locus for support of basic research in nutrient metabolism and energy expenditure as a foundation for disease-oriented studies. Consistent with its leadership role, the NIDDK is the organizational site for the Division of Nutrition Research Coordination (DNRC). Through the DNRC, the Nutrition Coordinating Committee provides the means for collaborative ventures throughout the NIH to encourage state-of-the-art nutrition research. The trans-NIH Bionutrition Initiative is such a venture, focusing on mechanisms underlying nutrient modulation of cell repair and maintenance of cell integrity. A majority of the NIH institutes is participating in the effort, as well as the Office of Research on Minority Health in the Office of the Director, NIH. A complementary initiative in bionutrition training is proposed which will enable nutritionists to learn new techniques in molecular biology. In like manner, molecular biologists will be encouraged to become familiar with nutrition questions.

To emphasize its research commitment to obesity as a total disease entity and a national public health problem, the NIDDK established the National Task Force on Prevention and Treatment of Obesity. The Task Force has recently examined research opportunities in obesity, which has resulted in a major plan for obesity research, entitled *"Towards Prevention of Obesity: Research Directions."* The plan elaborates a research agenda that moves in the direction of obesity prevention, while maintaining and encouraging vigorous research toward understanding the reasons for the increased prevalence of obesity in the U.S. The newly established Weight Control Information Network (WIN) will serve to enhance the transfer and translation of research findings concerning obesity and nutrition to clinical applications and public awareness. The NIDDK-supported program of Clinical Nutrition Research Units (CNRUs) and Obesity/Nutrition Research Centers (ONRCs) conducts basic and clinical research on obesity and nutrition. At one ONRC, graduate students working with Center investigators have been able to begin to study the spouses of women in the Women's Healthy Lifestyle Project. This research will determine whether a dietary intervention study, designed to modify fat intake in premenopausal women, will also indirectly affect the spouse's eating behavior, weight, and/or lipid levels. Studies such as this have been made possible through the presence of the ONRC which has helped investigators to recognize areas of common interest and led to new scientific interactions.

Obesity: In perhaps the greatest discovery in obesity research to date, NIDDK grantees have reported cloning the mouse *ob* gene, which results in profound obesity and non-insulin-dependent diabetes mellitus. They also have identified a human gene that is 84 percent homologous to the mouse gene. Initially, scientists located the gene by studying a strain of obese mouse. Once the *ob* gene was identified, it was used to pinpoint a nearly identical *ob* gene in human DNA. The normal mouse *ob* gene appears to be switched on in fat tissue, where it generates its protein product. Researchers believe the protein then is secreted into the bloodstream and, once it reaches the appetite-controlling area of the brain, acts to regulate food intake. It is in this way that the *ob* gene controls the balance of food intake required for energy expenditure. The mutant form of the *ob* gene may produce little or no protein and result in a lack of appetite control. Intake of more calories than are required for the amount of energy expended would lead to weight gain and fat deposition. Because of the close similarity between the human and mouse *ob* genes, it is likely that *ob* performs similar functions in both species. It is also likely that multiple genes and proteins may be implicated. Researchers are optimistic that these findings may lead to more effective medical therapies for weight problems, and to testing for genetic predisposition for obesity early in life. Once detected, dietary modification could help to mitigate the adverse effects of the mutant *ob* gene. Obesity prevention will in turn reduce the prevalence of many chronic diseases, including non-insulin-dependent diabetes, cardiovascular disease, certain cancers, gallstones, and stroke.

Kidney, Urologic, and Hematologic Diseases

The Kidney, Urologic, and Hematologic Diseases program of the NIDDK has primary responsibility at the National Institutes of Health for extramural research and research training in kidney, urologic, and fundamental aspects of hematologic diseases.

Kidney Diseases

The annual incidence of end-stage renal disease (ESRD) in the United States has been increasing steadily by nearly nine percent. In 1991, an estimated 230,000 Americans had ESRD, at a cost of approximately $8 billion, 72 percent of which was paid by the Federal government. Because of the large human and economic burden imposed by ESRD, the NIDDK supports considerable research aimed at preventing or delaying this irreversible kidney failure. The most frequent causes of ESRD are the kidney disease of diabetes mellitus, hypertension-related kidney disease, glomerulonephritis including IgA nephropathy, and renal cystic diseases.

Kidney Disease of Diabetes Mellitus (KDDM): Last year, investigators reported that a commonly prescribed medication for hypertension and heart failure significantly slowed the progression of kidney disease in patients with insulin-dependent diabetes mellitus. Continuing analyses of the results of this clinical trial have since shown that drug treatment lowered the protein excretion rate and lowered the risk of both ESRD and death, thus confirming the potential of such treatment to save lives, improve quality of life, and reduce health care costs.

Kidney Disease and Hypertension: According to the U.S. Renal Data System, kidney disease associated with hypertension is the most common primary diagnosis among African American ESRD patients. The African American Study of Kidney Disease and Hypertension (AASK) is currently evaluating whether lower than usual blood pressure control and/or certain classes of antihypertensive drugs can slow progression of kidney disease in African Americans. The NIH Office of Research on Minority Health also provides support for the AASK clinical trial, which includes more than 20 centers and involves all U.S. African American medical schools and most major metropolitan hospitals with a large African American patient population.

Evidence suggests that genes play a major role in determining the variation of blood pressure levels in the American population. However, genetic studies of hypertension are complicated by the likelihood that the most common forms of the disease are associated with the activity of many genes rather than a single-gene defect. This year, NIDDK grantees linked Liddle's syndrome, a rare, heritable form of hypertension, to a gene that encodes a subunit of the epithelial sodium channel. Mutations in that gene increase sodium reabsorption in the kidney. Because increased sodium reabsorption via this channel is associated with many types of secondary hypertension, the findings suggest that the Liddle's syndrome gene is a strong candidate for involvement in the more common forms of hypertension.

Other Clinical Trials: Other clinical research addressing the causes or treatment of ESRD include an investigator-initiated trial of prednisolone for the treatment of IgA nephropathy in children and young adults and an Institute-initiated trial to test the effects of higher hemodialysis doses and high flux on dialysis patient morbidity and mortality.

Autosomal Dominant Polycystic Kidney Disease (PKD): Research on PKD gained momentum this year with the identification of a PKD gene. The search for the gene was set in motion by NIDDK-supported studies that, in 1985, linked the genetic mutations in PKD to a region (PKD1 locus) of chromosome 16. That search has now culminated in the identification of a defective gene, at the PKD1 locus, by the European PKD Consortium. Identification of the PKD1 gene should make it possible to determine the normal role of the PKD1 protein in the cell and the mechanisms by which gene mutations cause the human disease.

Cell Surface Receptor for Calcium Ions: A major means by which cells receive information and instruction from their environment is through receptors that communicate with specific messengers such as hormones or neurotransmitters. Despite the variety of substances known to bind to cell receptors, until recently they all had in common that they were peptides, composed of amino acids. Now, NIDDK grantees have isolated and characterized the first example of a cell surface receptor that recognizes an inorganic ion, in this case, calcium. The discovery is likely to increase understanding of the function of the kidney and several other organs that have the newly discovered receptor. The investigators went on to show that mutations in the calcium receptor underlie two human genetic diseases of extracellular calcium balance: familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism.

Kidney and Urologic Research Centers: The NIDDK currently supports a total of 12 George M. O'Brien Kidney and Urological Research Centers and two Research Centers of Excellence in Pediatric Nephrology and Urology. Areas of research emphasis include chronic kidney disease, renal injury, congenital kidney disorders, glomerulosclerosis, nephrotic syndrome, developmental physiology of the kidney and urinary tract, urinary tract stone disease, and mechanisms of prostate growth. Three of the urology centers are supported by both the NIDDK and the National Cancer Institute and focus on prostate growth, both benign and malignant.

Urologic Diseases

Benign prostatic hyperplasia (BPH): BPH is the cause of the greatest number of surgical and diagnostic procedures in men. An ongoing NIDDK-supported clinical trial is evaluating the effects of two forms of medical therapy on progression of BPH, on reduction in surgery, and on pathologic changes in the prostate. Secondary studies will evaluate the relationship between BPH and the development of other prostate diseases, prognostic factors for BPH progression, and effects of concomitant health conditions such as hypertension and diabetes on prostate disease progression. Enrollment of a significant number of minority men with BPH will, for the first time, provide information on possible racial differences in the incidence and course of the disease.

Basic Bladder Research: Clues to the understanding and treatment of urinary tract disorders are likely to emerge from increased multidisciplinary basic research on bladder structure and function. For example, it has been known for some time that the lining of the urinary bladder in mammals has a highly specialized membrane that forms plaques. The plaques interact with cell surface structures and are believed to have a role in preventing the adherence of bacteria and the rupture of the bladder during distention. NIDDK grantees have identified several major protein components of these plaques in several mammalian species, including humans. With further research, the possible role of these "uroplakins" in bladder function and stability will be understood and should provide insights about disorders of the urinary bladder.

Women's Urologic Health: Disorders of the urinary tract, including urinary tract infection, urinary incontinence, and interstitial cystitis, are major health problems for women, resulting in a significant number of physician visits and hospitalizations. The NIDDK continues to encourage basic and clinical research on women's urologic health. The NIDDK-supported Interstitial Cystitis Data Base began patient recruitment last year. Initial data analyses will begin shortly, and, as more data accumulate, the Institute will begin to encourage investigators throughout the country to use both the data base and the associated tissue bank to help answer research questions about interstitial cystitis.

Hematologic Diseases

Platelet Growth Factor: Recently, NIDDK grantees reported the identification of thrombopoietin, a growth factor that stimulates the production of platelets. Patients with platelet defects or those receiving platelet-depleting chemotherapy or bone marrow transplantation are at serious risk of death from hemorrhage. Currently, they are treated with platelet transfusions. However, demand for platelets is increasing and their supply has been low. While a large number of factors regulating the formation of mature, circulating blood cells have been identified and studied extensively over the past several years, with several used in current clinical practice, platelet regulatory factors have remained elusive. Researchers have now cloned the cDNAs for both human and mouse thrombopoietin and have shown their effectiveness in vitro. Recombinant thrombopoietin was also effective in increasing platelet numbers in mice. The researchers expect that this platelet-regulatory factor will provide a basis for therapy of platelet deficiencies, much as erythropoietin, which stimulates the production of red blood cells, is currently used to treat anemia.

Gene Therapy: Hematologists have been leaders in developing the techniques of molecular biology that have enabled researchers to introduce healthy genes into the DNA of individuals with genetic defects. Although retroviruses have been used successfully as vectors for the transfer of genes into the human genome, they have the disadvantage of being able to infect all kinds of cells. This has been a major concern in current gene therapy, because of the possibility that a gene might be inserted where it could cause harm. NIDDK grantees recently reported a major step toward improving retroviral vectors by altering them so that they can target specific cells. Although the technique requires further work, it should have broad application and might eventually enable doctors to deliver genes to specific organs or tissues for the treatment of genetic diseases and cancer.

Molecular Hematology Centers: To accelerate progress in molecular hematology, the NIDDK has begun support of three Centers of Excellence in Molecular Hematology, Their programs focus on fundamental aspects of blood cell formation; strategies to correct inherited diseases of bone marrow-derived cells; and molecular regulation of iron and heme metabolism, cell adhesion, paroxysmal nocturnal hemoglobinuria, cell differentiation, and cytokine action.

Drugs for Hemoglobin Diseases: Work also continues on the development of drugs for the treatment of sickle cell disease and Cooley's anemia, and on the development of oral iron chelator drugs for patients with Cooley's anemia.

Intramural Research

Authorizing Legislation: Sections 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	
422	$79,970,000	445	$81,866,000	444	$85,180,000	-1	+$3,314,000

Nearly 250 research activities are under way in the NIDDK intramural research program at facilities in Bethesda, Maryland, and Phoenix, Arizona.

Funding for the Intramural Research program during the last five years has been as follows:

	Amount	FTE
FY 1991	74,559,000	428
FY 1992	79,653,000	457
FY 1993	82,449,000	453
FY 1994	79,970,000	422
FY 1995	81,866,000	445

Rationale for Budget Request

The FY 1996 budget estimate for the Intramural research program is $85,180,000, an increase of 4.0 percent over the FY 1995 estimate of $81,866,000 and a decrease of 1 in the number of FTEs. The fundamental research and clinical studies supported by the intramural research program help to provide a solid base of knowledge for the development of improved methods to treat and prevent disease. The following are examples of current research activities of the NIDDK Division of Intramural Research, and areas being expanded with FY 1996 funds.

G Proteins -- A 1994 Nobel Prize: The 1994 Nobel Prize in physiology or medicine was awarded to Dr. Martin Rodbell. While a scientist in the NIDDK intramural program, Dr. Rodbell discovered the phenomenon by which signals are transmitted from outside to inside the cell through the binding of GTP to what are known as G proteins. Since that discovery, Institute scientists have linked defects in G protein function to two serious endocrine disorders and have identified genetic mutations that are involved in those and other diseases associated with G protein abnormalities. Recently, they confirmed that the same G protein defect involved in the endocrine manifestations of McCune-Albright syndrome is also responsible for the crippling bone lesions seen in this disease.

Diabetes: Clinical studies have confirmed an association between high fasting free fatty acid concentration in the plasma and subsequent development of non-insulin-dependent diabetes mellitus (NIDDM) in the Pima Indians. The occurrence of two forms of fatty acid binding protein in this population appears to be one of several genetic polymorphisms that affect diabetes risk. Studies of the action of the binding protein will be pursued in 1996.

Obesity: Mexican Pimas, who have a less affluent, more traditional lifestyle than the Pimas in Arizona, also appear to have much less obesity and probably less NIDDM. The findings of a recently published study suggest that, despite a potential genetic predisposition for obesity, lifestyle changes including a greater energy expenditure in physical labor and a diet with less animal fat and more complex carbohydrates may be able to prevent the development of obesity or decrease its severity. Intramural studies of this population will address these prevention issues through participation in the NIDDM prevention trial in 1996.

Kidney Disease of Diabetes Mellitus (KDDM): Advanced glycosylation end-products (AGEs) are probably directly involved in the development of KDDM. Scientists have now shown that AGEs injected into healthy animals with normal blood sugar levels stimulate formation of connective tissue in the kidneys and over time lead to proteinuria, albuminuria, and advanced pathological changes in renal glomerular structure.

Mouse Model for Tay Sachs and Similar Diseases: A "Tay-Sachs mouse" has been developed in which the gene for one form of hexosaminidase (hexosaminidase A) has been disabled, and development is under way of a mouse model for Sandhoff disease, in which production of both forms of hexosaminidase (A and B) is altered. While the Tay-Sachs mouse shows the pathological changes typical of the human disease, the researchers believe that the Sandhoff mouse will also exhibit more of the clinical symptoms typical of both of these diseases in humans. NIDDK expects to significantly increase its work on such "Knockout gene" models in 1996.

Sickle Cell Disease and Beta Thalassemia: Industry's growing interest in, and various approaches to, the treatment of hemoglobin disorders make it increasingly likely that good medical treatments for hemoglobin disorders will be developed in the near future. This interest arose in large part from findings that the drug hydroxyurea could increase fetal hemoglobin and reduce the clinical effects of sickle cell disease. The NIDDK will continue its collaborations with three companies in 1996 to explore novel medical therapies for hemoglobin diseases.

Cancer-Related Research: Recently completed phase III trials indicate that recombinant human thyroid-stimulating hormone is safe and effective for use in diagnosing residual cancer cells after the thyroid has been surgically removed; a chemical with high affinity for sigma receptors has been shown to be a promising imaging agent for the detection of human tumors by positron emission tomography (PET) or single photon emission computed tomography (SPECT) scanning; and the structure of an important part of the p53 protein molecule (that domain which joins with three other p53 protein molecules to form the complex that binds to DNA and exerts the tumor-suppressor effect) has been determined.

Gene Regulation: Using the common antibiotic tetracycline and gene control elements from bacteria and a virus, investigators have developed a way to control the expression of specific genes in transgenic mice. With the new technique, the investigators plan to study in 1996 what happens when cancer-causing genes present in breast tissue become active.

Stroke: 1-Aminocyclopropanecarboxylic acid (ACPC), a compound shown by NIDDK scientists to prevent brain damage following stroke in animals is now being tested by industry in human Phase I trials. Continuing studies of ACPC at the NIDDK have recently indicated that the compound may also be useful for the treatment of spinal injury.

Drug Abuse: A promising compound was identified and tested in monkeys for the treatment of cocaine abuse. The potential usefulness of the compound is similar to that of methadone for the treatment of heroin abuse. In other studies, scientists seeking to develop a drug to stop the addictive process per se showed that ibogaine, which has been reported anecdotally to decrease addiction to a range of substances, may exert this anti-addiction effect by binding to the NMDA subtype of glutamate receptor. Because ibogaine blocked the receptor at pharmacologically relevant concentrations, the scientists are optimistic that it might be possible to develop an ibogaine-like drug that can target addictive behavior without unwanted toxic effects, and will be pursuing this research goal in 1996.

Mechanisms of Autoimmune Disease: Recent studies in an experimental model supported the hypothesis that hormonal suppression of major histocompatibility antigen class I (MHC I) is a normal mechanism to preserve tolerance to one's own tissues in the face of hormone-induced increases in tissue-specific products, such as thyroid hormone or insulin. Agents that have been associated with inducing or contributing to the autoimmune state, such as interferons, viruses, or stress, overcome this normal pattern by increasing MHC I expression. Consequently, autoimmune disease can result. MHC I-suppressive drugs may therefore be effective for the treatment of various autoimmune diseases.

Prion Disease: NIDDK investigators found that two yeast diseases are caused by prions. The existence of these yeast diseases indicates that prions are a more general phenomenon than previously thought, and the availability of a yeast model should facilitate the study of human diseases caused by prions.

National Institute of Diabetes and Digestive and Kidney Diseases

Research Management and Support

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1996 Authorization: Indefinite

FY 1994 Actual		FY 1995 Appropriation		FY 1996 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
175	$25,574,000	176	$25,990,000	176	$26,467,000	---	+$477,000

Support is provided through this activity for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, procurement, property control, and travel audit and control, which are most efficiently performed as centralized functions. Other functions included under this activity are the review, management, and negotiation of research and development contracts of the categorical program areas, translation of scientific findings to the medical community and members of the public, and the establishment of program plans to emphasize scientific opportunities identified by the national biomedical research community.

Funding for the Research Management and Support program during the last five years has been as follows:

	Amount	FTE
FY 1991	$21,295,000	165
FY 1992	24,470,000	172
FY 1993	24,052,000	170
FY 1994	25,574,000	175
FY 1995	25,990,000	176

Rationale for the Budget Request

The FY 1996 request for Research Management and Support is $26,467,000 and an employment level of 176 FTEs. This is an increase of $477,000 above the FY 1995 level of $25,990,000 and provides for the same number of FTEs as the FY 1995 level.

A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional and support personnel who are responsible for the administration of the Institute's grants activities. The staff assists in the planning and development of programs in research and training that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluates research and training grant applications for presentation to the NIDDK Advisory Council and provides required Council staff assistance; and serves as liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations.

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTE)

	1994 Actual	1995 Estimate	1996 Estimate
Office of the Director	67	68	68
Division of Diabetes, Endocrinology and Metabolic Diseases	19	19	18
Division of Digestive Diseases and Nutrition	16	16	19
Division of Kidney, Urologic and Hematologic Diseases	16	16	15
Division of Extramural Activities	57	57	56
Division of Intramural Research	422	445	444
Total	597	621	620

Average GS/GM Grade

1991	10.5
1992	10.5
1993	10.5
1994	11.0
1995	11.0
1996	11.0

Note: Includes FTEs associated with HIV Research Activities. Funds to suppor
FTEs are included in the NIH Office of AIDS Research.

National Institute of Diabetes and Digestive and Kidney Diseases

Program Administration
Detail of Full-Time Equivalent Employment

	1994 Estimate	1995 Estimate	1996 Request
Executive Level I..................			
Executive Level II.................	1	1	1
Executive Level III................			
Executive Level IV.................			
Executive Level V..................	1		
Subtotal.........................	2	1	1
Total - Exec. Lev. Sal...........	$212,181	$98,500	$100,100
ES-6...............................	1	1	1
ES-5...............................	3	3	3
ES-4...............................	14	13	13
ES-3...............................	2	2	2
ES-2...............................	2	2	2
ES-1...............................		1	1
Subtotal.........................	22	22	22
Total - ES Salary................	$2,337,800	$2,386,894	$2,425,084
GS/GM-15...........................	47	46	45
GS/GM-14...........................	50	48	47
GS/GM-13...........................	31	32	32
GS-12..............................	42	41	41
GS-11..............................	46	48	48
GS-10..............................	1	2	2
GS-9...............................	35	37	37
GS-8...............................	24	24	24
GS-7...............................	45	49	50
GS-6...............................	29	33	33
GS-5...............................	12	13	13
GS-4...............................	14	16	16
GS-3...............................	4	5	5
GS-2...............................	1	2	2
GS-1...............................	3	3	3
Subtotal.......................	384	399	398

Grades established by Act of July 1, 1944 (42 U.S.C. 207)			
Assistant Surgeon General	1	1	1
Director Grade	24	24	24
Senior Grade	5	5	5
Full Grade	17	17	17
Senior Assistant Grade	3	3	3
Assistant Grade	0	0	0
Subtotal	50	50	50
Ungraded	125	125	125
Total permanent positions	456	474	473
Total positions, end of year	583	606	605
Total full-time equivalent (FTE) employment, end of year............	597	621	620
Average ES level..................	3	4	4
Average ES salary.................	$102,969	$106,264	109,664
Average GS\GM grade...............	11	11	11
Average GS\GM salary..............	$45,350	$46,802	48,300

WITNESSES

Page
Alexander, Dr. Duane 2045
Amoruso, P.D 1811
Baldus, A.C 1727
Baldwin, Dr. Wendy 81
Barros, Colleen 737
Battey, Dr. James 903
Beldon, W.R 483, 591, 825, 903, 969, 1093, 1157, 1287, 1365, 1655, 1727, 1811, 1971
Berkowitz, S.J 301
Birkedal-Hansen, Dr. Henning 591
Bishop, J.M 1
Brown, Dr. L.J 591
Brown, M.S 1
Burgess, E.S 1445
Bursenos, S.J 1093
Carney, K.G 1365
Casady, Donna 2045
Cassman, Dr. Marvin 655
Chabner, Dr. Bruce 1811
Chamblee, Daryl 81
Cohen, Dr. L.K 591
Collins, Dr. F.S 1445
Counts, Dr. George 301
Cowdry, Dr. R.W 1157
Eastman, Dr. Richard 2139
Eiss, R.B 1093
Fauci, Dr. A.S 301
Ficca, S.A 1529
Fitzsimmons, W.T 1157
Fulton, B.E 2045
Goldrich, M.I 301
Gorden, Dr. P.E 2139
Gordis, Dr. Enoch 1027
Gottesman, Dr. Michael 81
Grady, Dr. P.A 969, 1727
Guerra, Maryann 483
Hall, Dr. Z.W 1727
Harlan, Dr. William 1529
Hartinger, J.P 1811
Hausman, Dr. S.J 825
Hodes, Dr. R.J 737
Hodgkins, G.E 655
Hubel, David 1

Page
Hurd, Dr. S.S 969
Johnson, Laurie 407
Jones, D.M 1287
Jordan, Dr. Elke 1445
Kerr, W.D 903
Kerza-Kwiatecki, M.S 825
Kirschstein, Dr. R.L 81, 825, 903, 1157, 1287, 1365, 1529
Kleinman, Dr. D.V 591
Kuffer, Dr. Carl 1655
Laurence, L.E 2139
Leasure, C.E., Jr 407
Lee, Dr. L.M 1529
Lenfant, Claude 483
Leshner, Dr. A.I 1287
Levine, S.U 1365
Lindberg, Dr. D.A.B 1365
Lipson, Carol 1655
Little, Francine 81
Lockshin, Dr. M.D 825
Long, Stephen 1027
Maddox, Y.T 2045
McGowan, Dr. J.J 301
McLaughlin, Dr. Jack 1655
McManus, Edward 1655
Menser, E.L 1093
Miller, H.R 1093
Millstein, R.A 1287
Moskowitz, Dr. Jay 903
Murray, J.E 1
Olden, Dr. Kenneth 407
Packard, Dr. Barbara 483
Paul, Dr. William 81
Pine, Martha 655
Pine, Richard 1157
Pinn, Dr. V.W 1529
Radebaugh, Dr. Teresa 969
Ramm, Dr. L.E 1971
Richardson, C.M 1027
Ross, K.S 737
Ruffin, Dr. John 1529
Russ, William 969
Schambra, Dr. P.E 1093
Schoolman, Dr. H.M 1365
Shafer, Dr. W.S 655
Shafer, R.L 1971
Sharp, P.A 1
Smith, K.A 1365
Snow, Dr. J.B 903
Sondik, E.J 1811
Sparks, P.T 903
Strachan, R.J 825
Summers, A.E 1971
Taylor, E.S 591
Trusty, M.K 1027

Page
Vaitukaitis, Dr. J.L 1971
Varmus, Dr. H.E 81, 301, 407, 483, 591, 655, 737, 969, 1027, 1093, 1445, 1529, 1655, 1727, 1811, 1971, 2045, 2139
Vennetti, J.C 1445
Watson, J.D 1
Wehling, James 483
Wetle, Dr. Terrie 737
Williams, D.P 81, 301, 407, 655, 737, 1027, 1445, 1529, 2045, 2139
Zellers, C.R 2139

INDEX

Nobel Laureates Biomedical Research Panel

Page
Aging 54
Applications of AIDS Research 61
Basic and Clinical Research 57
Budgetary Constraints 2
Budget Cuts, Impact on Research 47
Causes of Cancer, Environmental 60
Closing Remarks 79
Environmental Research 75
Health Care Delivery, Changes in 68
Introduction of Panel 1
Media, Role in Promoting Science 46
Minority Health, Research on 73
NIH Funding and Grants Awarded, Trends in 69
Opening Statements:
  Bishop, Michael 3
  Brown, Michael 11
  Hubel, David 19
  Murray, Joseph 25
  Sharp, Phillip 31
  Watson, James 37
Private Sector Research 77
Regulation, Impact on Research Costs 52
Research Priorities 62
Research Training 59
Role of NIH Funding 77
Science:
  Opportunities 76
    and Funding Sources 44
  Priorities 70
Treatment and Prevention 55
U.S. Research Compared to Other Countries 78

National Institutes of Health

OVERVIEW

Alzheimer's Disease:
  Investment in 124
  Research Progress in 123
Average Cost:
  Awards for Minority and Women Researchers 160–161
  History of Awards 159

Page
Average Length of Funding Research Projects 137
Behavioral Research:
  Elimination of Office on Behavioral and Social Sciences Research 176
  Funding for Behavioral and Social Science Research 133
  NIH Efforts in 105, 185, 186
Breast Cancer:
  Funding 164
  Research 114, 163–164
  Environmental Causes 115
Budget:
  Decrease in, Projections through FY 2000 94
Clinical Research:
  Extramural Funding for 136
  Peer Review of 104
  Response to IOM Recommendations 104
Clinical Trials:
  Funding 173–174
  Inclusion of Women 102
  Women and Minority Representation 103
Contracts with Commercial Institutions 125
Cooperative Research 170
CRADAs:
  Approval Process 132
  Research Support Through 127
Diagnostic Testing for Tuberculosis 172
Director's Discretionary Fund 133
Diseases Affecting Older Citizens 122
Disease Area Funding:
  Administration 136, 141, 185
  Funding Level for 156
Effects of FY 1995 Proposed Rescission 175
Facility Construction and Renovation 130
Financial Management Plan Revision 131
Genetic Research:
  Bioethics 157
  Clinical Applications of 108
  Heart Disease Discoveries 108
Grant Funding 137
Health Implication of FY 1996 Proposed Budget Cuts 177
Health Services Research 145–147
High Cost of Development of Animal Models 153
HIV/AIDS Research:
  Administration of 113
  Administration of Funding for 136
  Assessment of Administration Funding 175
  Budget Increase, at NIH 117
  Budget Priorities and Increase in Incidence Rates 119
  Coordination of 116
  Cross-over Benefits on Other Disease Areas 101
  Funding for 111
  Justification for Funding for 111
  Justification of the Budget Estimates 260–300
  Major Breakthroughs 99
  Prevention Efforts 155

Page

- Human Embryo:
  - Panel Recommendations for ... 139
  - Research ... 144
- Human Genome Project:
  - NIH Goals for ... 107
- Improving Health of the Nation's Citizens ... 178
- Indirect Cost ... 188
- Instrumentation and Equipment ... 130
- Intramural Research:
  - Federal Role in Supporting ... 181
  - Implementation/Recommendations from ... 138
  - Outside Funding for ... 128
  - Underwriting Funding ... 140
- IOM Recommendations, NIH Response to ... 104
- Issues Related to the RO1 Application ... 127
- Investment:
  - Effects of NIH Sponsored Research on Corporate ... 125
  - In Private Sector Collaboration ... 124
- Justification of the Budget Estimates ... 189–259
- Learning Disabilities Research ... 183
- Minority Health Issues ... 179–181
- Neurological Research Investment ... 178
- Neurofibromatosis Research ... 149
- Neuroscience Funding ... 179
- Number of Trained Research Scientists ... 96
- Nutrition Research ... 177
- Office of AIDS Research:
  - Role of Accomplishments of ... 113
- Opening Statement ... 82–86
- Office of Research on Minority Health ... 172–173
- Percent of Competing Awards by Race ... 162
- Positions:
  - Detail of End-of-Year Employment ... 130
  - Effect of Federal Downsizing of Senior Scientists ... 152
  - FTE Reductions ... 131
  - Impact of FTE Freeze ... 181
  - Senior Biomedical Research Service ... 128
  - Top Level Vacancies ... 127, 152
- Private Sector Investment in Biomedical Research ... 98
- Prostate Cancer:
  - Cancer Information ... 168
  - Clinical Trial Participation ... 168, 169
  - Funding ... 165
  - Prevalence Rates ... 165
  - Prevention Research ... 167
  - PSA ... 170
  - Rates Among African Americans ... 166
  - Research Programs ... 166
  - Screening Research ... 168
  - Summary ... 169
  - Tumor Genetics and Biology ... 167
  - Vaccine Research ... 167
- Public Education and Communication Efforts ... 95
- Public Health Education Partnership ... 183

Page

- Reasonable Pricing Clause 139
- Re-emerging Infectious Diseases 170–172
- Research:
  - RFAs vs Investigator-Initiated 141
- Research at Academic Institutions 124
- Research Priorities—Strategies for Setting 121
- Research Project Grants:
  - Average Length of 137
  - Recommended Funding Levels for 141
- Research Support:
  - Diabetes, Heart Disease, and Stroke 109
  - Per Death of Selected Diseases 112
- Set-Asides:
  - Initially Reserved for 17% Evaluation 134
  - Quality of Research Funded by SBIR 153
- Shannon Awards 132
- Sickle Cell Therapies 176
- Special Pay Authorities for Physicians 129
- Statement of the Director 87–93
- Streamlining Efforts 118
- Success Rates:
  - Competing Grant for African American Researchers 159
  - Competing Grant for HBCUs' 159
  - Competing Grant for Minority Researchers 158
  - Competing Grant for Women Researchers 159
  - For Young Investigators 97
  - Funding Needed for 30% 136
  - History of Research Project Grants 158
  - Minority and Women Researchers 158
  - Research Project Grants 158
- Support for Research at Academic Institutions 124
- Taps and Assessments 133
- Women's Health Initiative 119

National Institute of Allergy and Infectious Diseases

- AIDS:
  - Behavioral Research 347
  - Blocking Transmission 305, 330
  - Clinical Trials 331, 342, 344, 362
  - Definition 325, 351
  - Drug Development 331
  - Enrollment in Clinical Trials 352
  - FY 1996 Budget 324
  - HIV Research Plan 349
  - Incidence 325
  - Interleukin-2 ..... 302, 312, 349
  - Investment 313, 328, 329
  - Long-term non-progressors 307, 349
  - Office of AIDS Research 324
  - Relationship of AIDS and Center 327, 350
  - Relationsip of AIDS and Gene Therapy 349
  - Relationship of STDs and Contraction of AIDS 369
  - Research Focus 330, 335, 349, 351
  - Vaccines 323, 349, 350

Page

AIDS—Continued
  Women's Interagency HIV Study 351
Antibiotic Resistance 334
Asthma 308, 332, 335, 358
Award Rates 356
Chronic Fatigue Syndrome 308, 338, 344
Clinical Trials 352, 357, 361
Cost Savings Realized by Biomedical Research 303, 313, 361
Disease Prevention 305, 351, 365
Drug Resistant Microbes 334
Full Time Equivalent (FTE) Freeze 363
Gene Therapy 306
Haemophilus Influenza b 303, 306, 313, 323
Information Dissemination 361
International Health 338
Intramural Research 307, 342
Introduction of Witnesses 301
Justification of the Budget Estimates 370
Kidney Transplantation 359
Lyme Disease 302, 307, 337
Minority Health and Assistance:
  AIDS 352
  Enrolled in Clinical Trials 357, 362
  Historically Black Colleges and Universities 356
  Inner-City Asthma 333, 335, 358, 361
  Kidney Transplantation 359
  Participation in Biomedical Research 334
  Research Project Grant Average Costs 356
  Training of Minority Researchers 334, 356
NIAID Budget Decisions 329
NIH Budget Request 330, 339
Opening Statement 301, 305
Patents and Royalties 327
Re-emerging Diseases 315, 333, 365
Research Centers 345
Research Opportunities 348
Research Project Grants 355
Sexually Transmitted Diseases 305, 368
Topical Microbicides 354, 368
Tuberculosis 336, 366
Vaccines:
  Development 305, 323
  Initiative 360
Women:
  Health Research 351, 357
  HIV Interagency 351
  HIV Trials 362

National Institute of Environmental Health Sciences

AIDS Research 437
Alzheimer's Disease 448
Asthma 422, 439
Birth Defects 437

Page

- Breast Cancer:
  - Breast Cancer 445
  - Breast Cancer Gene 419
  - Long Island Breast Cancer Study 426, 427
- Cancer, Understanding Environmental Links 415
- Clearinghouse 429
- Clinical Trials 444
- Clinical Research 431
- Collaboration with Outside Groups 415
- Comparison with Other Agencies 416
- Cost-Benefit Requirements 417
- Electromagnetic Fields 424, 438
- Environmental Injustice 425
- Environmentally-Related Diseases in Children 423
- Facility Construction 423
- Federal Role in Intramural Research 447
- FTEs 444
- Gasoline Additives 447
- Justification of the Budget Estimates 450
- Lead Poisoning 423, 439
- Lead Clinical Trial 438
- Minority and Women's Health 443
- National Toxicology Program 430
- Opening Statement 407
- Parkinson's Disease 424
- Prostate Cancer 446
- Research Project Grants:
  - Constant Dollars 442
  - Racial Imbalance at NIH 443
  - Research Project Grants 440
  - Women and Minorities 441
- Risk Assessment 418
- Statement of the Director 410
- Streamlining 431
- Superfund 429
- Superfund Worker Safety Training:
  - Accreditation for Emergency Responders 436
  - Accreditation 433, 434, 435
  - Criteria, Development of 436
  - Criteria for Hazardous Waste Operations and Emergency Response 432
  - Employment 435
  - Evaluation 435
  - Minority Workers 433
  - Relationship Between Training and Work 421
  - Worker Training Programs 420, 448
- Testing Methods:
  - New 415
  - Use of Mammals in Testing 430

National Heart, Lung, and Blood Institute

- AIDS:
  - Research 537
  - Research Spin-offs 538

Page

Asthma:
  Advances in Treatment and Cure of Acute ... 520
  Self Management ... 525
Bone Marrow Transplantation ... 514
Clinical Trials:
  Significant Trials ... 534
  Information Dissemination ... 536
Competing Grants ... 503
Comprehensive Heart, Lung, and Blood Diseases Center ... 508
Education Programs ... 520
FTE Freeze ... 543
Graft Versus Host Disease ... 503
Heart Disease:
  Calcium Channel Blockers ... 524
  Cardiovascular Disease Deaths ... 506
  Cholesterol and Atherosclerosis ... 532
  Congestive Heart Failure ... 496
  Coronary Heart Disease ... 528
  Diet and Heart Disease ... 510
  Heart Attack in Women ... 545
  Strokes and Heart Attacks ... 519
  Vascular Stent Research ... 511
Hemophilia ... 497
Hypertension ... 530
Intramural Research, Federal Role in ... 543
Justification of the Budget Estimates ... 547
Lifestyle and Health ... 494, 506
Lymphangioleiomyomatosis ... 516
Mapping the Rat Genome ... 504
Minority Health:
  Health Disparities ... 499, 539
  Research ... 498
Obesity ... 494
Opening Statement ... 486
Research Areas ... 514
Research In Texas ... 507
Research Project Grants ... 541
Risk Factors ... 509
Sickle Cell Disease ... 503, 522
Sleep Disorders:
  National Center on ... 518
  Research ... 503, 533
Smoking ... 495
Statement of the Director ... 486
Streamlining ... 513
Transfusion Medicine:
  Blood Banking ... 517
  Transfusion Safety ... 533

National Institute of Dental Research

AIDS:
  Research Program ... 622
  Use of Saliva in Treatment ... 599
Biomaterials Research ... 606, 615

Page
Bone and Joint 612
Bone Clinic 599
Budget Estimates, Justification of 627
Clinical Trials 617
Collaboration 616
Craniofacial Birth Defects, New Research on 602
Designer Teeth 602
Fluoridated Water, Safety of 598
FTEs 620
Gene Therapy 606
Intramural Research, Federal Role in 620
Mercury-Containing Amalgams 603, 609
Minority Health 614
Minority Research Centers 600, 601
National Survey of Schoolchildren 601
Neurological Research 613
Opening Statement 591
Oral Cancer 607
Osteoporosis and Bone Conditions 624
Pain Killers, New Generation of 599
Pain Research, Progress in 610
Research Project Grants 618
Saliva as a Diagnostic Tool 623
Severe Caries in Infants 600
Statement of the Director 594
Women and Joint Disorders 624

National Institute of General Medical Sciences

Biotechnology Industry 670
Budget Estimates, Justification of 700
Budget Mechanism Table 704
Budget Reductions, Potential Impact of 666, 673
Collaborative Research and Development Agreements 687
Division of Cell Biology and Biophysics 724
Division of Genetics and Developmental Biology 719
Division of Pharmacology, Physiology, and Biological Chemistry 721
Division of Research Grants, Review of 670
Drug Discovery and Design 660
Food Additives Used in Animal Feed 685
General Statement Justifying Budget 716
Historically Black Colleges and Universities 688, 692, 695, 697
Minorities in the Life Sciences 663
Minority Health 686
Minority Programs:
    Bridges Program 684, 686
    Funding Level for 675, 683
    Minority Access to Research Careers Program 669, 675, 677, 683, 684, 692–695, 727
    Minority Biomedical Research Support Program 669, 676, 683, 695–697, 726
    Minority Opportunities In Research Division 669, 675, 687, 726
    Special Initiatives 727
Minority University and College Enrollments 678
Opening Statement 655
Ph.D.s Awarded to Minorities in the Life Sciences 678

Page
Polymerase Chain Reaction (PCR) 661

Research:

- Accomplishments 680
- Acquired Immune Deficiency Syndrome 716
- Areas of Opportunity 662
- Average Cost of Research Grants 690
- Basic Research Goals 680, 716
- Breast Cancer Research 698
- Cancer Research 672
- Cellular Research 685
- Economic Impact of Research 661
- Extramural Research Program 719
- Molecular Research 666
- Intramural Research Program 729
- Prostate Cancer Research 673
- Research Management and Support 731
- Research Project Grants 688
- Research Training 667
- Significance to Industry 671
- Success Rates 668, 688, 689
- Trauma and Burn 671
- Women and Minorities in Research 682, 688–691

Statement of the Acting NIGMS Director 660

Training:

- Biotechnology Training 670, 687
- National Academy of Sciences Report on 698
- NRSA Training Levels 683, 698
- Numbers of Trainees 683
- Preparing Future Scientists 663
- Research Training 667
- Research Training Pipeline 682
- Stripend Levels 677
- Women and Minorities in Research Training 682

National Institute on Aging

Aging Issues 765
Aging Research 764, 778
AIDS Research 782

Alzheimer's Disease:

- Alzheimer's Disease Research 745, 760, 764, 769
- Alzheimer's Disease Education and Referral Center 759
- Alzheimer's Disease Centers 759

Baltimore Longitudinal Study of Aging 752
Behavioral Research 753
Breast and Prostate Cancer 774
Budget 780, 783, 790
Caloric Restriction 749
Cancer and the Elderly 781
Cardiovascular Research 762
Demography Research Centers 752
Diabetes 775, 786
Frailty in the Elderly 776
Health and Retirement Study 751
Intramural Research 757

Page
Justification of Budget Estimates 790
Longevity 754
Minority Health 756, 772
Neurological Research/Alzheimer's Disease 771
Nursing 788
Opening Statement 737
Prevention 787
Research Centers 759
Research Priorities 745
Research Project Grants 783
Special Populations 772
Statement of Director 740
Stroke 755
Success Rates 750
Telomeres 750, 781
Women's Health 773, 788

National Institute of Arthritis and Musculoskeletal and Skin Diseases

AIDS Research, Impact on Other Diseases 859
Average 862, 863
Basic Science 835
Budget Estimates, Justification of 866
Calcium 864
  Calcium Intake 839
  Calcium Consensus Development Conference—Public Education Efforts ... 840
Clinical Trials 843
Disease Registries 842
Disparities In Health Care 849
Epidermolysis Bullosa 857
Exercise in Health, Role of 848
Fibromyalgia 848
Funding For Diseases 851
Gene Therapy To Treat Skin Diseases 842
Hip Replacements 838, 855
Inherited Disorders of Connective Tissue 848
Juvenile Arthritis 844
Low Back Pain 846, 854
Minority Health 858
Neurosciences Research 857
Opening Statement 825
Opportunities 860
Osteoarthritis 844
Osteoporosis 852
  Hyperthyroid and Osteoporosis 839
Potential For Overlapping Research 855
Repetitive Motion Disorders 854, 856
  Injuries 842
Research Centers 851
Research Priorities 838
Rheumatic Diseases, Novel Therapies for 840
Rheumatoid Arthritis, Antibiotics to Treat 841
Skin Diseases 857
Skin Ulcers 846

Page
Statement of the Acting Director ... 828
Success Rates ... 861, 862, 863
Systemic Lupus Erythematosus ... 845
  Genetic Links to Lupus ... 847
Lupus and Women's Health ... 865

National Institute on Deafness and Other Communication Disorders

Clinical Trials:
  Clinical Trials ... 918, 930
  Cooperative Group ... 922
Cochlear Implants ... 914
Fetal Hearing Development ... 925
Hair Cell Regeneration ... 914
Hearing:
  Impairment ... 912
  Impairment in the Aging ... 926
  Impairment Resource Registry ... 916
Justification of the Budget Estimates ... 936
Minority Support ... 935
Noise-Induced Hearing Loss ... 925
Opening Statement ... 904
Otitis Media ... 915, 927
Partnership Program ... 921, 930
Research:
  Advancements ... 924
  Genetic ... 916, 925
  Hearing Aid ... 918, 920, 929
  Minority ... 919
  Neuroscience ... 929
  Olfactory ... 912
  Review of, Program ... 912
  SBIR-Supported Research ... 928
RPG Average Costs ... 933
Special Emphasis Areas ... 922
Statement of the Director ... 906
Success Rates ... 931, 932
Tinnitus ... 913

National Institute of Nursing Research

AIDS ... 984, 985
Alzheimer's Disease ... 980, 984, 989
Asthma ... 987
Breast Cancer ... 994
Community-Based Investigations ... 977
Disease Prevention in Rural Populations ... 979
Elderly and the Oldest Old ... 990
Establishing Healthy Behaviors in Younger Children ... 994
Genetic Screening ... 995
Home Care ... 993
Hysterectomy ... 995
Justification of the Budget Estimates ... 997
Minorities in Research ... 990
Minority Health Programs ... 986

Page
National Nursing Research Agenda 976
Nursing Schools 981
Opening Statement 970
Program Goals: National Institute of Nursing Research 976
Research on Pain 982, 989
Research Opportunities 991
Staffing Levels at NINR 982
Statement of the Acting Director 972
Success Rates 983
Tuberculosis 983
Women's Health Research 979

National Institute on Alcohol Abuse and Alcoholism

Alcohol and Disability 1037
Alcohol, Estrogen, and Osteoporosis 1042
Alcohol Related Birth Defects 1036
Alcohol Research in Genetics 1036
Alcoholism and Birth Defects 1061
Alcoholism Treatment: Medications Development 1053
Breast Cancer and Alcohol 1042
Budget Estimates, Justification of 1065
Clinical Trial Funding 1055
Community Prevention Trials 1050
Disabilities from Alcohol 1038
Distinct Genetic Underpinnings of Alcoholism 1047
Economic Toll of Alcohol Misuse 1063
Fetal Alcohol Syndrome 1045
Fetal Alcohol Syndrome and Ethnicity 1046
Fetal Alcohol Syndrome: Prevention and Research 1048
Liver Disease 1042
Medications Development 1047
Moderate Alcohol Consumption 1051
Moderate Consumption 1040
Moderate Drinking 1041
Moderate Drinking, Research on 1041
Moderation and Breast Cancer 1064
Naltrexone 1039
Opening Statement 1027
Patient Treatment Matching 1049
Prevention 1063
Prevention and Treatment 1062
Progress in Alcohol Research 1034
Research Dissemination 1046
Research Opportunities 1056
Statement of the Director 1030
Success Rates and Average Cost Trends 1058
Treatment for Alcoholism 1048
Treatment Matching and Genetics Cooperative Agreement 1053
Trends in Consumption Among Youth 1056
Women's Health 1061
Women's Health Issues 1064

Page

Fogarty International Center

AIDS 1101
Biodiversity 1105
Cooperative Efforts 1104
Downsizing 1106
Downsizing Issues 1111
Environmental Hazards 1122
Environmentally-Induced Diseases 1126
Eradication of Polio Worldwide 1115
FIC Long-Range Plan 1108
Funding From Other Sources to FIC Initiatives 1108
Justification of Budget Estimates 1129
Middle-East and Environmental Issues 1128
Minority Research Support 1102
New and Emerging Infectious Diseases 1103
NIH Support of Foreign Research and Foreign Scientists 1116
Opening Statement 1093
Program on Environment and Health 1112
Program on Population and Health 1111
Re-Emerging Infectious Diseases 1120
Reproductive Health 1127
Research Project Grants 1123
Sentinel System for Infectious Disease 1113
Statement of the Director 1096

National Institute of Mental Health

Affective and Anxiety Disorders 1187–1189
AIDS Research 1177
Basic Neuroscience and Behavior 1163–1164, 1206
    Hormones and Behavior 1191–1197
    New Animal Model 1214
    Behavioral Research Task Force Report 1176–1177
    Behavioral Science and Disorders 1191, 1226–1228
    Neurological Research 1206
    Neural Basis of Communication 1197–1199
Brain Imaging 1158
Breast Cancer and Mental Health 1229
Childhood Mental Disorder 1163, 1204, 1220
    Service needs 1214–1215, 1226
Clinical Trials 1217–1219
Costs of Mental Illness 1158
Eating Disorders 1159, 1189–1190, 1209
Genetic Factors 1159, 1220
Hispanic Research Center 1171–1172, 1180–1181, 1199–1201
Human Brain Project 1210–1211
Intramural Research 1206–1207
Justification of the Budget Estimates 1254–1286
Lab Tests 1215
Medications for Mental Illness 1184–1187, 1204–1206
    Effectiveness for 1205–1206

Page

Medications for Mental Illness—Continued
  Prescribing Medications (by non-M.D.s) ... 1205
  Prozac ... 1204–1205
Minority Research ... 1206–1207, 1216–1217
  Historically Black Colleges and Universities ... 1223, 1225
Nobel Laureates, Testimony of ... 1167, 1176, 1206, 1215–1216
Opening Statement of Acting Director ... 1157–1160
  Prepared statement and biography ... 1161–1166
Peer Review System ... 1174–1175
Prevention Research ... 1177–1178
Reinvention ... 1210
Research:
  Cost Savings from ... 1161–1162
  Funding ... 1206, 1213–1214, 1221–1225
  Opportunities ... 1219–1220
  Questioned ... 1167–1171, 1178
    List of Questioned Projects ... 1169–1170
    Nature of Attack on NIMH ... 1170–1171
    Nature of Investigations and Project Length ... 1179–1180, 1183–1184
    NIMH's Response ... 1183–1203
  Support for ... 1176
Services Research ... 1210
Schizophrenia ... 1158, 1162–1163, 1212–1214
Sex Offender Treatment Study ... 1173–1174, 1230–1253
Transsexual Study ... 1171, 1199

National Institute on Drug Abuse

Adolescent Health ... 1319
AIDS and Drug Abuse ... 1302
Drug Abuse:
  In Adolescents ... 1298, 1326
  In Rural Areas ... 1296
  In youth ... 1301
  Prevalence of ... 1300
Drug Addiction as Illness ... 1326
Drug Addiction Treatment:
  Clinical Research and Drug Addiction Treatment ... 1299
  Gene Therapy ... 1303
  Pharmacologic Treatments ... 1302, 1316, 1328
  Treatment for Pregnant Women ... 1325
Drug Free School Program ... 1302
Drug Use Research Among Hispanics ... 1306
Extent of Drug Problem ... 1312
Fetal and Child Development ... 1299
Funding Allocations:
  Behavioral versus Biomedical Research Funding ... 1305
  Prevention Research Funding ... 1319
  Justification of the Budget Estimates ... 1332
Molecular Cloning ... 1313
Nature of Addiction ... 1296
Needle Exchange Program ... 1297
Neurological Research ... 1320
Opening Statement ... 1287

Page

Research Advances:

- Basic Research ... 1314
- Clinical Research ... 1315
- Epidemiological Research ... 1315
- HIV/AIDS ... 1316
- Medications Development ... 1315
- Prevention ... 1316

Research Project Grants ... 1321
Statement of the Director ... 1290

National Library of Medicine

Basic Library Services ... 1384
Bioethics ... 1382, 1387
Computer Literacy ... 1385
Disease Treatment ... 1379
Electronic Medical Record System ... 1383
High Performance Computing ... 1380, 1387, 1390, 1395, 1404
Human Genome ... 1382
Information Superhighway ... 1378, 1400
Integrated Advanced Information Management Systems ... 1389
Internet ... 1392
Justification of the Budget Estimates ... 1410
Opening Statement ... 1365
Opportunities ... 1405
Outreach ... 1378, 1397
Reinvention Laboratory ... 1394
Research Grants ... 1408
Statement of the Director ... 1365
Unified Medical Language Systems ... 1385
User Fees ... 1381
Visible Human Project ... 1380, 1405

National Center for Human Genome Research

Application of Knowledge ... 1492
Breast Cancer ... 1493
Collaborations ... 1491
CRADA with Genetic Therapy, Inc ... 1486
Curriculum Vitae ... 1455
Definitions of Sequencing and Mapping ... 1484
Delaying the Human Genome Project ... 1474
Department of Energy Role in the Human Genome Project ... 1487

Discrimination:

- Discrimination as a Consequence of Genetic Testing ... 1464
- Status of Legislation About Genetic Discrimination ... 1471
- Use of Genetic Information ... 1461

DNA Sequencing ... 1480
Employment Issues and Genetic Information ... 1471
Ethical, Legal, and Social Implications ... 1474, 1490
Gene Identification ... 1458
Gene Discovery to Treatment ... 1460
Gene Identification ... 1458
Genetic Counselors Training Program ... 1488
Human Embryo Research ... 1476

Page
Intellectual Property 1485
Justification of the Budget Estimates 1497
Legal and Ethical Implications of Genome Research 1457
Mouse Map 1491
National Resource, NCHGR as a 1493
Opening Remarks 1445
Outreach 1491
Patenting Issues 1482
Privacy Issues 1472
Prostrate Cancer 1494
Protection of Genetic Information 1472
Research Grants 1495
Research Guidelines 1476
Staffing Levels 1488
Statement of the Director 1450
Status of Laws 1462
Targeted Chromosomes 1460
Technology Transfer 1483, 1489

Office of the Director/Buildings and Facilities

AIDS Research 1577
Clinical Center:
    Budget by Major Components 1561
    Minorities and Women in 1579
    Renewal 1556
    Replacement 1545
Consolidated Laboratory Building 1563
Construction:
    Fund 1565
    Future Campus 1545
    Unobligated Balances 1542
Diversity 1569
EEO Rating Criteria 1588
Extramural Associates Program 1587
Fact Finding Team 1587
Fire Station 1565
Indirect:
    Costs 1547, 1574
    Costs for Facilities 1549
Inpatient Occupancy Rate 1562
Intramural Research 1586
Justification of Budget Estimates 1590
Loan Repayment and Scholarship Programs 1573
Master Plan/Facilities Revitalization 1554
Minority Health Initiative 1544, 1581
Office of Alternative Medicine 1570
Office of Behavioral and Social Sciences Research 1580
Opening Statement 1529
ORMH Pilot Projects 1576
Profusion of Specific Offices 1543
Public Outreach 1542
Research Grant:
    Outcomes of Applications 1575
    Top 100 Colleges and Universities Receiving Funding 1551

Page
Statement of the Deputy Director 1535
Transfer Authority 1571
Uncommitted Unobligated Balance 1566
Women's Health:
  Curriculum 1571
  Initiative 1567, 1584
  Planned Initiatives 1546

National Eye Institute

25th Anniversary 1663
Administrative Supplements 1668
AIDS Research 1672
Approval of Surgical Procedures 1664
Cataract 1668, 1676, 1680
Clinical Trials 1669, 1681
Contact Lenses 1670
Cost Savings 1674, 1681
Decade of the Brain 1667, 1679
Diabetes 1679
Diabetic Retinopathy 1686
Dissemination of Clinical Trial Results 1671
Eye Movement Disorders 1671
Federal Role in Intramural Research 1683
FY 1994–1996 Budget 1678
FTEs 1683
Gene Therapy 1665, 1680
Information Dissemination 1664
Justification of Budget Estimates 1687
Lasers 1669
Low Vision Aids 1671
Minority Health 1672
National Diabetes Month 1666
National Eye Health Education Program 1676
Neuritis and Multiple Sclerosis 1686
Neurological Research 1666
Opening Statement 1655
Radial Keratotomy 1663
Research Impact on U.S. Industry 1676
Research Project Grants 1682, 1684
Retinopathy of Prematurity 1663
Spin-offs 1681
Statement of the Director 1658
Strabismus 1670
Stroke Research 1667
Treatment of Eye Disease 1673
Vitrectomy 1674

National Institute of Neurological Disorders and Stroke

Average Costs 1770
Batten Disease 1739
Birth Defects 1745
Brain Imaging 1737, 1761
Calcium Channel Blockers 1745

Page
Clinical Trials 1765
Collaborative Efforts in Brain Research 1758
Competing Grant Average Costs for African American Researchers in Current and Constant Dollars 1773
Competing Grant Average Costs in current and Constant Dollars 1770
Decade of the Brain 1743, 1763
Dissemination of Results 1766
Duchenne Muscular Dystrophy 1738, 1759
Funding for Specific Diseases 1747
FY 94 Competing Grant Average Costs by Gender in Current and Constant Dollars 1772
Gender Differences in the Brain 1742
Huntington's Disease 1757
Justification of the Budget Estimates 1774
Minority:
  FY 94 competing Grant Success Rates for Minority Researchers 1771
  Minority and Women Applicants—Average Costs 1772
  Minority and Women Applicants—Success Rate 1771
Multiple Sclerosis 1760
Nerve Injury 1760
Neuro-AIDS and Cancer Research 1767
Neurogenetics 1734
Neurological Disorders in Children 1768
Opening Statement 1728
Parkinson's Disease 1748
  New Treatment for Parkinson's Disease 1758
  Parkinson's Disease Research 1749
Research Centers 1747
Review of NINDS Programs 1757
Statement of the Director 1732
Stroke 1763
  Aspirin 1740
  Stroke in African Americans and Hispanics 1741
  Stroke in Hispanics 1744
Success Rates 1770

National Cancer Institute

Abortion and Breast Cancer 1852
African-American Males and Cancer 1864
African-Americans and Cancer 1858
AIDS Research 1881
  Application to Other Cancer Research 1885
  AIDS-Related Malignancies 1884
  AIDS Vaccine Development 1883
  HIV Research 1882
Applications of AIDS and Breast Cancer Research 1887
Appointment of New Directors 1839
ASSIST Program 1844
Average Cost of RPGs to Women and Minorities 1896
Behavior Modification 1824
Biography 1837
Boron Neutron Capture Therapy 1835
BRCA–1 and BRCA–2 1862
Breast Cancer 1827, 1862

Page
Breast Cancer —Continued
  Causation ... 1828
  Detection ... 1823, 1827
  Funding ... 1854
  Incidence ... 1828
  Research Funding ... 1841
By-Pass Budget ... 1854
Cancer Centers ... 1849
Cancer Control ... 1851
Cancer Screening ... 1859
Cancer Incidence ... 1826
Cancer and the Environment ... 1878
Children and Cancer ... 1889
Colon Cancer Detection ... 1840
Colorectal and Prostate Cancer ... 1864
Construction Funds ... 1843
Designer Therapies ... 1872
Diet and Cancer ... 1874
Diet Modification ... 1825
Diet and Cancer In African-American Females ... 1877
DOD Breast Cancer Research Program ... 1848
Earmarks ... 1842
Environmental Justice Initiative ... 1898
Evaluation of the National Cancer Program ... 1871
FCRDC Intramural Research ... 1847
Four Leading Cancers ... 1858
Genetic Discrimination ... 1855
H. Pylori ... 1904
Immunology Research and Tuberculosis ... 1881
Information Dissemination ... 1824
Justification of Budget Estimates ... 1906
Leukemia Treatment Research ... 1829
Long Term Outlook ... 1822
Long Island Breast Cancer Study ... 1839
Lung Cancer ... 1821
Mammography ... 1825
Mammography Guidelines ... 1845
Melonoma and Sun Exposure ... 1831
Melanoma Vaccines ... 1830
Metastasis Prevention ... 1830
Minority Health ... 1892
National Action Plan on Breast Cancer ... 1863
National Surgical Adjuvant Breast and Bowel Project ... 1838
Natural Products Screening Program ... 1850
NCI Breast Cancer Budget ... 1853
Opening Statement ... 1811
Overall Progress Against Cancer ... 1821
Pancreatic Cancer ... 1901
Phytochemicals ... 1832
Prostate Cancer Treatment ... 1822, 1869
Prostate Cancer Research ... 1864
Prostate and Breast Cancer Detection ... 1822
Prostrate Cancer Funding ... 1871
Proton Beam Construction ... 1843

Page
RAS Inhibitors 1847
Relationship Between Cancer and AIDS Research 1832
Research Project Grants 1894
Screening Tests for BRCA–1 Mutations 1844
Spending on Various Cancers 1844
State of the Institute 1837
Statement of the Director 1815
Success Rate of Minority Research Applications 1895
Treating Tumors with Boron 1833
War on Cancer 1858
Women and Intramural Research at NCI 1843

National Center for Research Resources

National Center for Research Resources 1971
Academic Health Centers and Managed Care 2014
AIDS and Breast Cancer 2003
Alzheimer's Disease 2006
Animal Facility Improvement 1997
Bioengineering Initiative 1998
Biomedical Research Support 1988
Biomedical Research Technology Centers 1989
Clinical Research 1996, 2001
Clinical Research Ombudsman 2014
Cost Benefit 2002
Diabetes 2007
Extramural Construction 1980
Funding for Specific Programs 1988
Gene Vector Laboratories 1996
General Clinical Research Centers 1980, 2012
High Performance Computing 1981
Indirect Costs 2000
Institutions Infrastructure 2000
Justification of Budget Estimate 2015
Minority Programs 1983
NCRR Reorganization 1998
Opening Statement 1971
Pipeline 2001
Research Centers in Minority Institutions 2008
Shared Equipment 1998
Shared Instrumentation 1995
Shared Resources 1994
Statement of the Director 1971, 1975
Synchrotron Facilities 1981
Virtual Reality 1982

Natural Institute of Child Health and Human Development

Access for Persons with Disabilities 2067
Add HEALTH Study 2069, 2072
AIDS Research 2046, 2055, 2088
Barrier Contraceptives 2056
Behavioral Research 2071
Bionutrition and Pregnancy 2062
Birth Defects 2056, 2079

Page
Breast Cancer 2054
Child Care 2063
Children's Diet and Behavior 2065
Children's Health 2079
Chronic Fatigue & Blood Pressure 2093
Contraceptive and Infertility Research Centers 2059, 2069
Diagnosis Through Computer Assisted Imaging 2061
Funding for Research Areas 2069
Hispanic Health 2054
HIV Transmission from Mother to Child 2057
Human Embryo Research 2053, 2059
Infant Mortality 2081
Justification of Budget Estimates 2096
Medical Rehabilitation Research 2066, 2070, 2074
Minority Health 2083
Neurological and Behavioral Research 2091
Newborn Screening for HIV 2058
Opening Statement 2045
Opportunities 2086
Perinatology Research Branch 2060
Research Centers 2069
Research Project Grants 2094
School-Based Intervention Programs 2063
Smoking and Infertility 2064
Statement of the Director 2048
Status of the Health of Children 2067
Substance Abuse in Pregnancy 2068
Sudden Infant Death Syndrome 2046, 2064, 2075
Survey of American Sexual Behavior 2060
Teenage Pregnancy 2062
Vaccines 2045, 2065, 2077
Violence Research 2073, 2088
Vitamin Research 2084

National Institute of Diabetes and Digestive and Kidney Diseases

AIDS Research 2174
Budget Estimates, Justification of 2180
Centers 2159
Clinical Trials 2173
Cystic Fibrosis 2162
Cystic Fibrosis Therapy 2145, 2149
Diabetes 2149, 2151, 2166, 2177
Diabetes and Cardiovascular Disease 2154
Diabetes and Immunology 2146
Diabetes and Public Education 2157
Diabetes and Stress 2155
Diabetes Clinical Research 2153
Diabetes Genes 2156
Diabetes Prevention and Treatment Initiative 2165
Diabetes Research Plan 2172
Diabetes—Progress in Treatment 2148
Diabetes—Economic Cost 2147
Duodenal Ulcers 2177
FIAU Clinical Trial 2156, 2178

3 9999 05570 749 9

Page
Funding for Selected Disease Areas 2159
Gene Therapy 2166
Genetic Causes of Diabetes 2165
Inflammatory Bowel Disease 2160, 2163
Insulin Resistance 2170
Interstitial Cystitis 2146
Juvenile Diabetes 2164
Kidney Failure 2171
Minority Health 2172
Non-Insulin Dependent Diabetes 2164
Obesity 2160, 2170
Opening Statement 2139
Polycystic Kidney Diabetes 2150, 2154, 2164
Program Balance 2145
Research Grant Success Rates 2152
Research Project Grants 2175
Statement of the Director 2141
Type II Diabetes 2162
Weight-Control Information Network 2163

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